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Studies on the Renal Excretion of Radioactive Digitoxin in Human Subjects with Cardiac Failure

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Randomly labeled C^{14}-digitoxin was used in a quantitative study of the renal excretion of unchanged digitoxin and its metabolites in three human subjects with cardiac insufficiency. The elimination of approximately 60 to 80 per cent of an administered dose through the kidney suggests that the major route of elimination of digitoxin in cardiac patients is through the urinary route. There is a marked initial excretion of digitoxin during the first two days after administration of the radioactive drug followed by a gradual leveling off of the excretion gradient thereafter. Minute amounts of unchanged digitoxin have been detected in the urine up to the fortieth day after administration of a single dose of the glycoside, while C^{14}-labeled compounds were detected up to the seventy-fourth day.

UNTIL RECENTLY, the lack of suitable analytic methods has hindered quantitative studies of the renal excretion of digitalis glycosides. Utilizing only bioassay technics, early investigators[1–5] concluded that little if any of the various glycosides studied was excreted in the urine of various species of laboratory animals after oral or parenteral administration. Recently, however, Friedman and co-workers,[6–9] employing the sensitive embryonic duck heart method, reported that rats, rabbits and dogs excrete negligible amounts of digitoxin in the urine while normal human subjects excrete up to "40 per cent of a digitalizing dose of digitoxin in a physiologically active state" over a period of 12 to 24 days. In 1950 Geiling and co-workers[10] using radioactive digitoxin, reported that dogs excrete up to 46 per cent of a single dose of the glycoside in the urine. More recently, Fischer and associates,[11] also using radioactive digitoxin, have shown that rats and cats eliminate 30 per cent and 55 per cent, respectively, of unchanged digitoxin and metabolites through the urinary route. Clinically, it has been assumed that cardiac patients either excrete or destroy 0.1 to 0.2 Gm. of digitalis or 0.1 to 0.2 mg. of digitoxin per day.

To gain further information concerning the mode of elimination of digitoxin in human subjects, renal excretion studies have been conducted in cardiac patients using digitoxin uniformly labeled with carbon[14]. Use of the tracer technic permits not only greater sensitivity for the detection of minute amounts of the labeled drug, but it also enables one to follow the metabolic products of the parent

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compound. Furthermore, the method enables one to distinguish between unchanged digitoxin and other possible cardioactive principles. By the tracer method it is possible to assay as little as 0.02 microgram of radioactive digitoxin.

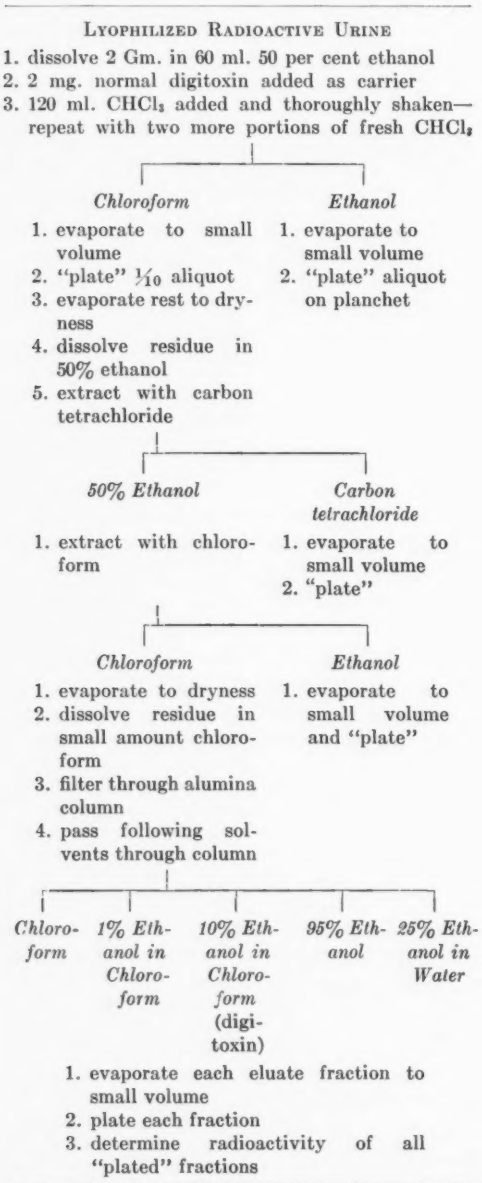

Fig. 1. Flow-sheet of extraction procedure

The present communication is in the nature of a preliminary report. Results presented herein indicate that the major route of elimination of digitoxin in human subjects with cardiac failure is through the renal system.

Method

Three patients with heart disease were selected for this study on the basis of their willingness and ability to cooperate. All three subjects had arteriosclerotic heart disease with congestive failure of varying degrees of severity. Subjects E. W., a 58 year old male weighing 67.6 Kg., and E. S., a 71 year old male weighing 61.5 Kg., had auricular fibrillation. Subject O. L., a 65 year old woman weighing 54.2 Kg., had a sinus rhythm. Throughout the period of study all patients were hospitalized in the metabolic ward of Billings Hospital where a constant diet and a constant intake of distilled water was administered. Records of the basal pulse rate, both apical and radial, and body weight were made each morning with the patient in the post-absorptive state. Prior to the administration of the labeled digitoxin, digitalis was withheld for varying lengths of time. In the case of O. L. this period was six days, for E. W. 14 days, and for E. S. 34 days.

Subjects O. L. and E. W. were then given a single intravenous dose of 0.5 mg. of the labeled digitoxin and subject E. S. a dose of 1.5 mg. Twenty-four hour urine samples were collected during the period of observation which varied for each subject. For O. L. this period was 12 days, for E. W. 23 days and for E. S. 84 days. Urine samples were stored under refrigeration during the 24 hour collection period and then lyophilized by the freeze-dry method. During the period of observation in E. W. no cardiac glycosides or diuretic agents were given. In the case of O. L., 0.5 mg. of digitoxin (Eli Lilly) was administered four days after giving the labeled digitoxin, and 15 days later a mercurial diuretic was administered as symptoms and signs of congestive failure supervened. Subject E. S., who received the largest dose of radioactive digitoxin, was given 1.5 mg. of digitoxin (Eli Lilly) 29 days after receiving the labeled dose. Electrocardiograms were taken at one to three day intervals.

The radioactive drug administered to the patients was prepared by biosynthesis with *digitalis purpurea* plants exposed to an atmosphere of carbon[14] dioxide. Extraction and purification of the glycoside was performed by initial solvent extractions followed by the use of chromatographic methods for the ultimate isolation of digitoxin as a single entity.[12] Specific activity of two batches of the labeled drug used in this study was 525,000 counts per minute per milligram or 0.364 microcurie per milligram and 620,000 counts per minute per milligram or 0.430 microcurie per milligram.

The extraction procedure employed for the isola-

tion of unchanged digitoxin and fractionation of its metabolic products from lyophilized urine of cardiac patients receiving uniformly labeled carbon^{14}-digitoxin is shown on the flow-sheet in figure 1. Radioactivity determinations of the various extracted fractions were made by an internal gas-flow Geiger counter.[13] Self-absorption, dilution and background corrections, was made on the counting data. Using a known amount of radioactive digitoxin as a control and subjecting it to the extraction procedure described in figure 1, recoveries of 97 ± 2 per cent have been obtained.

The various radioactive fractions extracted from the urine of cardiac patients were divided into three categories: "unchanged" digitoxin, chloroform soluble metabolites, and water soluble metabolites. "Unchanged" digitoxin was found in the 10 per cent ethanol in chloroform eluate. The word "unchanged" is placed in quotation marks since conventional identification and characterization methods could not be employed for the compound due to the minute amount of drug recovered from the urine. The chloroform soluble metabolites occurred in all the various fractions obtained from the original chloroform soluble residue other than the 10 per cent ethanol in chloroform eluate. The water soluble metabolites occurred in the original 50 per cent aqueous ethanol solution. The significance of the chloroform soluble metabolites lies in the fact that they may be closely related in structure to the parent compound, while the water soluble metabolites are in all probability conversion products of digitoxin. It should be noted that the metabolic compounds were not isolated and characterized as single entities but only fractionated according to their solubility properties and chromatographic behavior on an alumina column.

Several tests were used in the identification of the "unchanged" digitoxin recovered from the urine of cardiac patients. Comparison of R_f values of the radioactive drug with nonradioactive crystalline digitoxin (Lilly) by paper partition chromatography[12] indicated that the two compounds were identical. Also polarographic analysis of the reisolated digitoxin in 50 per cent ethanol gave a half-wave potential of −1.95 volts which is within the published range of −1.934 to −1.988 volts.[14] Color reaction tests with a p-dimethylaminobenzaldehyde reagent gave a specific blue color for both the radioactive drug and normal digitoxin. The use of the isotope dilution method for determining a constant specific activity of a compound also confirmed the presence of digitoxin in the 10 per cent ethanol in chloroform eluate.

Results

Clinical Effects

In subjects E. W. and E. S., who were fibrillating, the basal pulse rate responded to the administration of the radioactive digitoxin in a manner very similar to that effected by the nonradioactive digitoxin. Figure 2 shows the basal pulse rate record of E. S. Subject O. L. had no significant effect on the basal pulse rate. The serial electrocardiograms in subjects E. W. and E. S. reflected the effect of the administered doses of digitoxin by a slowing of the ventricular rate but with only insignificant changes in the S-T segments and T waves. O. L.'s serial electrocardiograms responded to the radioactive preparation and to the nonradioactive drug by exhibiting a temporary partial heart block and numerous ventricular premature systoles.

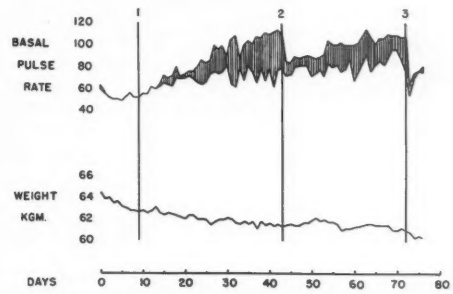

FIG. 2. Basal pulse rate of subject E.S. (1) Digitalis discontinued; (2) 1.5 mg. C^{14} digitoxin I.V.; (3) 1.5 mg. nonradioactive digitoxin (Eli Lilly) I.V.

Experimental Effects

The daily renal excretion rates of "unchanged" digitoxin and its metabolic products for the three cardiac subjects who received a single intravenous dose of radioactive digitoxin are shown in figures 3 and 4.

The term "microgram equivalent" noted in the charts is used to express the amount of original drug converted into the metabolic products, that is, if 1 microgram of radioactive digitoxin has a certain number of disintegrations per minute and if a metabolic product of the drug contains the same number of disintegrations per minute, then the metabolite is considered to amount to 1 "microgram equivalent." It should be stressed that the term "microgram equivalent" does not express the actual amount of the metabolic product but only the equivalent amount of C^{14} converted from the parent compound.

1. Persistence

It can be seen from results shown in figures 3 and 4 that the injected radioactive digitoxin is excreted over a considerable period of time. Data showing the persistence of the drug in the three subjects are summarized in table 1. Although the experimental periods for both subjects O. L. and E. W. were not of sufficient duration, extrapolation of the excretion curves indicates that the drug persists in the body for about 31 to 42 days. Subject E. S., who was studied the longest and received the largest dose, was still excreting "unchanged" digitoxin in the urine up to the fortieth day

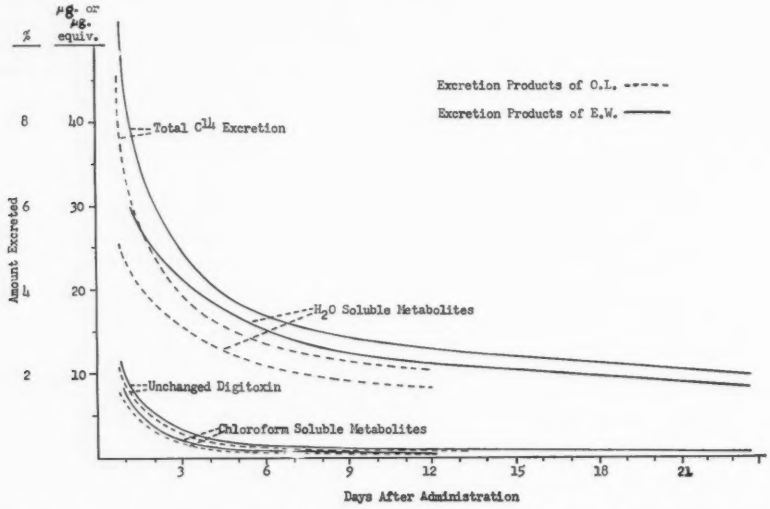

FIG. 3. Daily renal excretion rates of C^{14}-digitoxin and its metabolic products for subjects O.L. and E.W.; dose, 0.5 mg. I.V.

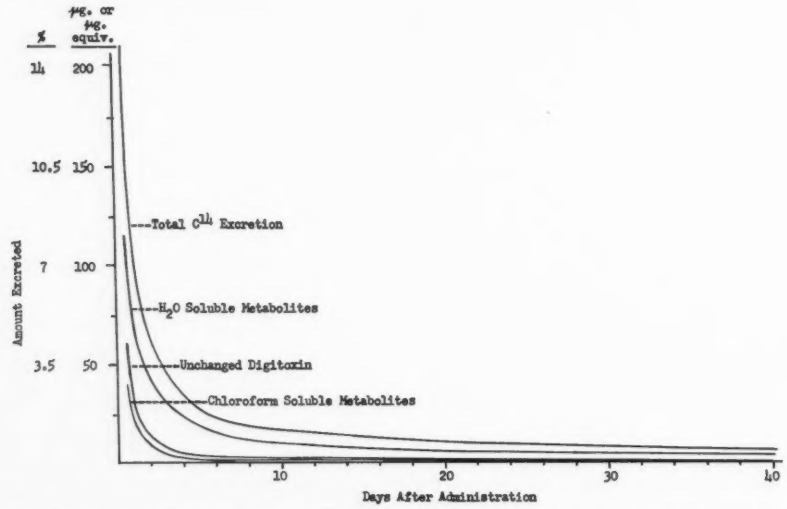

FIG. 4. Daily renal excretion rates of C^{14}-digitoxin and its metabolic products for subject E.S.; dose, 1.5 mg. I.V.

after administration of the drug, while it's radioactive metabolic products were detected up to the seventy-fourth day.

2. Excretion Gradient

The relatively rapid elimination of the cardiac glycoside during the first three days after its administration is noteworthy. As illustrated by the curves in figures 3 and 4, there is a very rapid initial loss during the first three days followed by a gradual leveling off after the seventh and eighth days. During the initial three-day period, 20 per cent of the administered dose is eliminated with about half of this amount being excreted during the first 24 hours. In the case of the "unchanged" digitoxin there is approximately five times as much drug eliminated during the first 24 hour period as there is during the second 24 hour period. Analyses of the first 24 hour urine samples at six hour intervals show that most of the "unchanged" digitoxin eliminated during the first day is excreted during the initial six hours.

3. Comparison between "Unchanged" Digitoxin and its Metabolites

Another significant finding was the relatively small amount of "unchanged" digitoxin eliminated through the renal route in comparison with the larger amount of metabolic products. (See table 2.) Although experimental periods for both O. L. and E. W. were not of sufficient duration, extrapolation of their excretion curves indicate that less than 9 per cent of the digitoxin would have been excreted unchanged. Subject E. S., who received three times the dose of the first two subjects, excreted less than 10 per cent of the administered drug as "unchanged" digitoxin. In all three patients only 4 to 8 per cent of the original drug was excreted as chloroform soluble metabolites while 34 to 68 per cent was excreted as water soluble metabolites. Excluding the data from subject O. L., since her experimental period was too short, 62 to 79 per cent of the administered drug was excreted through the urinary route. This suggests that the kidneys act as

TABLE 1.—*Length of Time Required for Excretion of Various Radioactive Compounds after Single Administration of C^{14}-Digitoxin*

Subject	Dose (mg.)	No. of Experimental Days	Excretion Products		
			"Unchanged" Digitoxin	$CHCl_3$-soluble Metabolites	H_2O-soluble Metabolites
O. L.	0.5	12	*27 ± 2 days	*17 ± 2 days	*38 ± 4 days
E. W.	0.5	23	*25 ± 2 days	14 days	*35 ± 4 days
E. S.	1.5	85	†40–50 days	†40–50 days	†74–85 days

* Figures estimated by extrapolation of excretion curves.
† Urine of intermediate days not collected.

TABLE 2.—*Amount of Various Radioactive Compounds Excreted during Experimental Period after Single Administration of C^{14}-Digitoxin*

Subject	Dose (mg.)	No. of Experimental Days	Excretion Products							
			"Unchanged" Digitoxin		$CHCl_3$ Sol. Metabolites		H_2O Sol. Metabolites		Total Excretion	
			%	μg.	%	*μg.	%	*μg.	%	*μg.
O. L.	0.5	12	5.6 ± 0.10	28.3 ± 0.5	3.9 ± 0.14	19.6 ± 0.7	33.6 ± 1.5	168 ± 7	43.1 ± 1.5	216 ± 7.4
E. W.	0.5	23	6.8 ± 0.11	34.4 ± 0.5	3.9 ± 0.14	19.5 ± 0.7	68.1 ± 3	341 ± 15	78.9 ± 3	394 ± 15
E. S.	1.5	85	9.6 ± 0.10	144 ± 1.2	8.0 ± 0.8	120 ± 2	†44 ± 1	†672 ± 11	†62 ± 0.8	†933 ± 7

* μg. equivalent of C^{14}-digitoxin.
† Figure indicates amount excreted up to fortieth day, urine not collected daily thereafter.

the main excretory route for the elimination of digitoxin and its metabolic end products.

4. Excretion Ratio between Metabolites and Digitoxin

In figure 5 is illustrated the metabolite-digitoxin ratio curve as calculated from the cumulative excretion rates at various intervals after the single administration of digitoxin. It will be noted that the metabolite-digitoxin ratio of the two subjects who received 0.5 mg. of digitoxin increases much more rapidly on successive days than it does for the subject who received a dose three times as large. This seems to indicate that over a given period there is a greater percentage conversion of

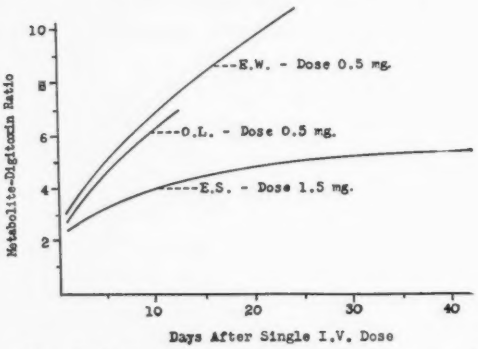

FIG. 5. Ratio of metabolites to digitoxin excreted at various intervals and its relationship to dosage.

digitoxin to its metabolic products with a small dose than with a larger one.

It is also interesting to note that during the first 24 hours the metabolite-digitoxin ratio is relatively low, whereas with an increase in the time interval there is an increase in the ratio.

DISCUSSION

The renal excretion rate of uniformly labeled carbon^{14}-digitoxin and its metabolic products in human subjects with cardiac insufficiency has been studied using the extremely sensitive isotope tracer technic.

Contrary to the concept held by many of the earlier investigators,[3, 4, 15, 16] the major route of excretion of digitoxin in human beings seems to be through the kidneys and not by way of the liver and gastrointestinal tract. This is supported by the fact that approximately 60 to 80 per cent of the administered dose is eliminated through this route either in the form of "unchanged" digitoxin or its metabolic products.

However, in some animals, the major route of digitoxin excretion seems to be through the gastrointestinal tract. Recently, Fischer and co-workers[11] have reported that rats (digitoxin-resistant animals) excrete most of the drug through the gastrointestinal tract, while cats (digitoxin sensitive animals) excrete it about equally between the renal and gastrointestinal system. In light of these facts and those of the present investigation, there is the possibility that the more sensitive an animal species is to digitoxin the more likely it will be to excrete a larger portion of the drug through the kidneys.

Probably the main reason why many of the earlier investigators placed so little importance on the kidneys as the major route of excretion is attributable to the fact that they had no way of measuring the large amount of metabolic products excreted in the urine. Our data indicate that 52 to 72 per cent of the original drug was excreted as either chloroform or water soluble metabolites. Only 6 to 10 per cent of the drug was excreted as "unchanged" digitoxin.

In 1919, Pardee[17, 18] reported that the body was able to excrete a uniform amount of the drug daily which did not depend upon the quantity in the body. Gold in 1923[15] and more recently Friedman and his associates[8] presented evidence that this is not the case and reported that the amount excreted daily was dependent upon the amount in the body. Our results confirm the findings of Gold and of Friedman.

Schmiedeberg in 1883[19] theorized that the prolonged effect of digitoxin was due to the storage of the drug in the tissues of the body and to its slow excretion. Since the work of Hatcher in 1912[20] this has been generally accepted, although there has been no incontrovertible evidence of the persistence of the drug in the body until the recent work of Friedman and his co-workers.[8] This group reported that a "digitalizing" dose of digi-

oxin persisted in the body from 12 to 24 days after a single administration of the glycoside. Our studies indicate that unchanged drug is still excreted in the urine up to 40 days after an intravenous administration of 1.5 mg. of the radioactive drug. Degradation products of digitoxin were detected up to the seventy fourth day. However, the significance of the excretion of metabolites after the fortieth day is difficult to evaluate since it is possible that the radioactivity in the metabolites may come from compounds resynthesized from the one- and two-carbon fragment pool.

To elucidate this point further, urea was isolated from urine of patients receiving digitoxin and recrystallized a minimum of eight times. With an ionization chamber[21] as the method of assay, urea samples from all three patients showed radioactivity. Specific activity of the urea ranged from 7 dps to 10 dps per gram of sample. Recently Hellman and Eidinoff[22] cited evidence that the carbon of urea is derived from the carbon dioxide pool, which is chiefly in the form of carbonic acid. This would therefore suggest that at least part of the digitoxin molecule is broken down into one-carbon fragments, permitting the resynthesis of various biochemical compounds. However, due to the extremely low specific activity of the urea, its radioactivity could not be detected with a windowless gas flow geiger counter. It will be recalled that all the metabolic products mentioned previously were detected with this type of counting device. Therefore, it would seem reasonable to believe that since urea could not be detected by the latter method, compounds resynthesized from one- and two-carbon fragments would also be undetected due to their extremely low specific activity. For this reason it is believed that since the metabolic products cited in our data are of sufficient specific activity, they may be conversion products of carbon 14 digitoxin and not necessarily compounds resynthesized from the body carbon dioxide pool.

The nature of the prolonged retention of the glycoside in the body is not apparent from the data. Such investigators as H. Fischer, Lendle and others have cited the ability of tissue proteins to bind cardiac glycosides. It is highly possible that there may be various types of tissue proteins to which the drug can bind reversibly, with some proteins binding the glycoside more tenaciously than others. This persistence also adds support to the concept of cumulative action of digitoxin as observed by clinicians.

Little is known as yet concerning the nature of the metabolic end products. Due to the minute amount of radioactive metabolites excreted in the urine it is not possible at the present time to chemically identify and characterize the metabolites. However, biologic tests will be made on the metabolites to test them for their cardiotonic activity.

Presently further investigation on the renal excretion of digitoxin is being conducted on a larger sampling of cardiac patients.

Summary

1. Using the isotope tracer technic, a quantitative study was made of the renal excretion of intravenously administered radioactive digitoxin in three human subjects suffering from cardiac insufficiency.

2. The elimination of approximately 60 to 80 per cent of an administered dose through the kidneys suggests that the major route of elimination of digitoxin in cardiac patients is through this route.

3. There is a very marked initial excretion of digitoxin during the first two days after administration of the glycoside followed by a gradual leveling off of the excretion gradient after about the fifth day.

4. A minute amount of "unchanged" digitoxin is detected in the urine for as long as 40 days after administration of a single dose of radioactive digitoxin, while carbon^{14}-labeled compounds can be detected up to the seventy-fourth day.

5. Most of the carbon^{14} from the labeled drug is eliminated as metabolic products while only 6 to 10 per cent of the original drug is excreted as "unchanged" digitoxin.

6. The cumulative effect of digitoxin appears to be related to its persistence in the body.

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SUMARIO ESPAÑOL

Digitoxima rotulada con C^{14} fue usada en un estudio cuantitativo de excreción renal de digitoxina no alterada y sus productos metabólicos en tres sujetos humanos con insuficiencia cardíaca. La eliminación de aproximadamente 60 a 80 por ciento de la dosis administrada por medio del riñón sugiere que la ruta mayor de eliminación de la digitoxina en pacientes cardiacos es por la vía urinaria. Hay una marcada excreción de digitoxina durante los dos primeros días despues de administración de la droga radioactiva seguido de una nivelación gradual de la pendiente de excreción más luego. Cantidades minutas de digitoxina no alterada han sido descubiertas en la orina hasta el cuadragésimo día después de la administración de una sola dosis del glicósido, mientras que substancias rotuladas con C^{14} fueron percibidas hasta el día septuagésimo cuarto.

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The Effects of Hexamethonium on Certain Manifestations of Congestive Heart Failure

By Robert T. Kelley, M.D., Edward D. Freis, M.D., and Thomas F. Higgins, M.D.

Hypotensive doses of hexamethonium were administered intravenously to 19 patients with various types of heart disease in congestive failure. Clinical improvement as judged by the usual methods was seen in most cases. Intracardiac or pulmonary artery pressures paralleled the fall of arterial pressures following hexamethonium in four patients with hypertensive heart disease in congestive failure. It is suggested that hexamethonium, by reducing the total peripheral resistance and by a redistribution of blood volume, may interrupt the vicious cycle of heart failure.

FAILURE of the circulation is associated with a number of interrelated factors tending to aggravate it and perpetuate its existence. It is generally accepted that low output failure leads to an increase in peripheral resistance due to reflex vasoconstriction.[1] The increased peripheral resistance in turn adds to the work of the failing heart, thereby further decreasing its output.

In addition, diminished cardiac output mechanically induces a redistribution of total blood volume toward the larger veins of the circulation.[1] There is some evidence that constriction of smaller postarteriolar vessels may contribute to the venous engorgement.[1] The failing right heart is then subjected to excessive filling pressures, producing a further decrease in output. Thus, a vicious cycle is established. Diminished cardiac output induces increased peripheral resistance and central venous congestion, both of which add further loads to the failing heart (fig. 1).

The therapeutic measures thus far available to interrupt this cycle have been directed at improving the function of the heart itself with digitalis, increasing the excretion of salt and water by use of mercurial diuretics, and direct reduction of venous engorgement by venesection or venous tourniquets. At the present time there are no recognized methods of lowering the peripheral resistance, thereby reducing the work of the failing heart, or of redistributing the total blood volume. This study was undertaken with a view toward decreasing the peripheral vascular resistance and central engorgement, using hexamethonium, a ganglionic blocking agent.[2]

Materials and Methods

Nineteen patients with different types of heart disease in various degrees of congestive failure were studied at the Veterans Administration and Georgetown University Hospitals, Washington, D. C.

Peripheral venous pressure was measured in the antecubital vein with a saline manometer. The zero point was placed on a plane 10 cm. above the skin of the patient's back. In seven cases a polyethylene catheter was inserted into the antecubital vein and advanced to the level of the subclavian. Decholin was the indicator used in measuring the arm-to-tongue circulation time. The vital capacity was determined by means of a McKesson-Scott Vital Capacity Apparatus. The blood pressure was measured by the auscultatory method. These procedures were employed immediately before the slow intravenous administration of hexamethonium and immediately after a satisfactory hypotensive response to the drug was observed.

From The Cardiovascular Research Laboratory, Georgetown University Hospital, the Department of Medicine, Georgetown University School of Medicine, and the Veterans Administration Hospital, Washington, D. C.

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Dr. Kelley is a Research Fellow of the Washington, D. C. Heart Association.

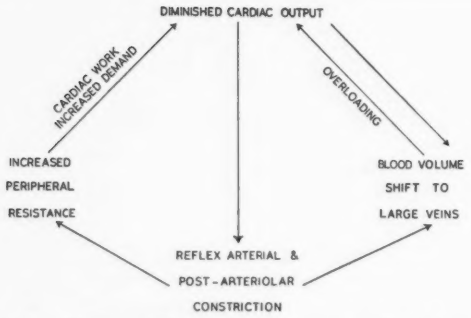

FIG. 1. Chart illustrating the suggested "vicious cycle" hypothesis in low output heart failure. (See text for further details.)

$\left(\frac{\text{sytolic} + 2 \times \text{diastolic}}{3}\right)$ arterial pressure was 35 mm. Hg. In all cases with an elevated venous pressure there was a significant reduction following hexamethonium (table 1), the range being from 40 to 133 mm. water and the mean 82 mm. water. Patients with normal levels of venous pressure initially exhibited less significant and consistent reduction. The most striking results were seen in cases with hypertensive heart disease and aortic valvular disease.

Of 12 patients with an initial arm-to-tongue circulation time in excess of 20 seconds, eight

TABLE 1.—*Effect of Hexamethonium on the Manifestation of Congestive Failure in Patients with Various Types of Heart Disease*

Patient		Age	Sex	Type of Heart Disease	Degree of Orthopnea	Vital Capacity in Liters	Venous Pressure mm. H_2O	Circulation Time in Seconds	Heart Rate per Min.	Blood Pressure mm. Hg	Amount of Hexamethonium mg.
Bre	Before	50	M	Hypertensive	None	1.9	168	20.5	88	240/150	65
	After					2.2	35	19.5	74	168/120	
Rol	Before	49	M	Hypertensive	0	2.6	174	22	102	230/130	50
	After				0	3.2	180	32	93	195/115	
Has	Before	53	F	Hypertensive	+++		385	45	80	200/130	17.6
	After				+++		290	27	80	105/70	
Che	Before	44	F	Hypertensive	None		175	25	79	230/140	25
	After						100	12	71	170/105	
Bro	Before	59	M	Hypertensive	None	2.0	132	27	107	230/140	25
	After					2.2	115	20	95	145/90	
Ups	Before	79	M	ASHD	++	1.6	180	44	70	150/100	45
	After				++	1.6	130	20	74	106/70	
Sim	Before	57	M	RHD with AS	+++	2.8	175	25	98	105/65	20
	After			& AI	++	3.0	60	16	79	80/50	
Tay	Before	24	M	Myocarditis	None	2.8	90	25	107	112/75	75
	After					2.75	50	17	107	90/60	
Fre	Before	57	M	Hypertension	+++	1.0	170	47	115	190/140	25
	After				+	1.0	90	45	110	120/90	
Ste	Before	56	M	Hypertension	++	2.6	184	40	90	160/130	30
	After				0	2.95	115	29	71	120/80	
Shi	Before	54	M	ASHD	+		250	45	115	120/80	17.5
	After				+		140	25	110	94/68	
Rol	Before	64	M	Syphilitic	++	0.8	170		107	165/85	15
	After				+	1.1	85		115	140/60	
Har	Before	37	M	RHD with MS	None	1.8	140	23	75	118/80	15
	After					1.8	140	23	120	90/65	
Whi	Before	59	M	Hypertension	++	1.55	110	16	100	180/110	10
	After				0	2.1	70	16	100	145/85	
Tro	Before	51	M	ASHD	None		140	19	80	120/75	8
	After						130	19	75	80/50	

RESULTS

The average dose of hexamethonium was 30 mg. and the average fall of "mean" manifested a reduction ranging from 26 to 54 per cent (mean 42 per cent). Of the other four cases, three showed little or no change and one

exhibited an increased circulation time. In the two patients whose circulation time was less than 20 seconds during the control period no further reduction occurred.

The heart rate slowed in 12 of 19 cases studied. The range of deceleration was 5 to 24 beats per minute with an average slowing of 12 beats per minute. There was no change in heart rate in four and an increase in three cases. However, despite the lack of slowing, the majority of these cases exhibited evidences of improvement in their circulatory status as judged by venous pressure and/or circulation time measurements. Two of the three patients who manifested an increase in heart rate had auricular fibrillation. The first, who had arteriosclerotic heart disease, showed a slight increase in rate. The second patient, who had mitral stenosis in the compensated phase, exhibited an increased ventricular rate from 75 to 120 beats per minute when the blood pressure fell. In this patient, in contrast to the others, there were no significant changes in the other functions studied.

The vital capacity improved in 5 of 11 patients in whom determinations were made. The remainder showed no significant change. Twelve cases manifested various degrees of orthopnea. In eight such individuals there was improvement in their respiratory embarrassment which was so marked and rapid that in several instances the patients commented on their relief during the test procedures without having the question presented to them. Cheyne-Stokes respirations cleared in the single patient who exhibited this type of breathing.

Aside from the general tendency towards slowing of the heart rate in the presence of normal sinus rhythm, the electrocardiographic tracings disclosed slight prolongation of the Q-T interval in 8 of 14 cases. Minor T-wave deviations occurred in six instances. In the cases of auricular fibrillation mentioned above there was slowing of the "f" waves as seen best in lead V_1 with a resultant increase in ventricular responses similar to that seen frequently following quinidine or procaine amide.

TABLE 2.—*Changes in Right Heart and Pulmonary Arterial Pressures in Patients with Hypertensive Heart Disease in Failure Treated with Hexamethonium*

Patient		Age	Sex	Amount of Hexamethonium (mg.)	Systemic Arterial Pressure (mm. Hg)	Heart Rate per Min.	Right Heart Pressures (mm. Hg)	Degree of Orthopnea
Dew	Before	52	M	150	215/140	116	50 (PAP)	++++
	After				165/115	92	40	+
Lum	Before	40	F	37	210/140	100	30 (RAP)	+++
	After				164/100	92	23	+
Ash	Before	59	M	31	160/120	80	30 (RAP)	++++
	After				120/90	65	20	++
Cle	Before	53	M	8	225/125	91	115/25 (RVP)	+++
	After				173/87	91	85/15	±

(PAP) indicates pulmonary arterial pressure, (RAP) right auricular pressure, and (RVP) right ventricular pressure.

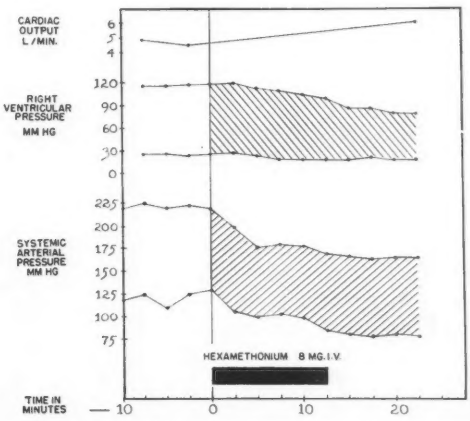

FIG. 2. Chart showing an increase in cardiac output and decrease in right ventricular and systemic arterial pressures after, as compared to before, the intravenous administration of 8 mg. of hexamethonium ion to Cle, a white male, age 53, with hypertensive heart disease in congestive failure.

Cardiac catheterization studies were carried out in four patients with hypertensive heart disease in severe congestive failure (table 2). In each instance there was a decrease in intracardiac or pulmonary arterial pressures which paralleled the fall in arterial pressure. Cardiac output, as determined by the direct Fick method, was performed in one case with heart failure (fig. 2). Following hexamethonium there was an increase in cardiac output, a fall in total peripheral resistance and a decrease in right ventricular pressure. In all instances there was dramatic symptomatic improvement in breathing.

Discussion

It is a common observation that venesection or the application of venous tourniquets may produce immediate relief of symptoms in low output types of heart failure. When this procedure is performed, the venous pressure decreases but the arm-to-tongue circulation time remains essentially unchanged.[3] According to McMichael and associates,[3] following venesection the blood pressure almost always falls in the presence of an increased cardiac output, indicating a decreased peripheral resistance.

Several workers[4, 5] have observed that aminophylline similarly reduces elevated venous pressure. Howarth, McMichael and Sharpey-Schafer observed that the fall in right auricular pressure after aminophylline was comparable to that following the pooling of blood in the lower extremities using tourniquets, but there was a greater increase in cardiac output which was attributed to aminophylline's direct action on the myocardium. The effects were most readily observed in hypertensive heart failure.

During the hypotensive response to veratrum viride an increase in cardiac output and a decrease in pulmonary arterial pressure were observed to occur in hypertensive heart failure.[6] Others,[7, 8] using tetraethylammonium, which blocks transmission of impulses through peripheral autonomic ganglia, demonstrated a fall in venous and arterial pressures both in hypertensive and nonhypertensive heart failure. There were no consistent changes in arm-to-tongue circulation time. Hayward[7] as well as Lyons[9] noted decrease in dyspnea but this was not observed by Relman and Epstein.[8]

Priscoline, an adrenolytic and sympatholytic drug, also produced a decreased venous pressure in patients with congestive heart failure. However, the heart rate fell only in cases of cor pulmonale.[10] Dresdale and his associates also observed in patients with primary pulmonary hypertension a more marked decrease in pulmonary vascular resistance following Priscoline than after tetraethylammonium.[11] Perhaps Priscoline has some special effect in patients with heart failure associated with primary pulmonary hypertension.

It seems apparent that a variety of agents and procedures will produce a definite fall in venous pressure, right auricular and pulmonary arterial pressures when there is elevation initially. However, in contrast to results from venesection and with tetraethylammonium, the circulation time following hexamethonium improved. This is in keeping with a more complete return toward compensation in a failing heart.

Clinically in the long term therapy of severe hypertension using hexamethonium it has been observed that congestive heart failure when present is easier to control, and in occasional cases it has been possible to discontinue digitalis and mercurial diuretics.[12]

It is suggested that hexamethonium may interrupt the congestive failure cycle at two points: (1) by decreasing the total peripheral resistance the work demand on the left ventricle is lessened and (2) by reducing the filling pressure of the right heart the overloaded right ventricle is able to contract more effectively. The mechanism by which the right heart pressures diminish cannot be definitely established at present. It seems probable, however, that several factors may act conjointly. First, the increased output of the left ventricle resulting from the decreased peripheral resistance produces an unloading of the congested right heart and central veins. Second, blockade of vasoconstrictor reflexes may increase the vascular capacity as a

consequence of peripheral vasodilatation, particularly of the postarteriolar vessels, thus producing a redistribution of the total blood volume.

These data supply additional suggestive evidence that the degree of constriction of the peripheral vessels may have an important influence on the function of the failing heart as originally suggested by McMichael.[13] In addition, the beneficial effects of hexamethonium suggest that the adverse vasocontriction which occurs in heart failure may be under neurogenic control.

Since the conclusion of our study there has appeared a series of papers by Brod and Fejfar in which the authors observed the effects of the adrenergic blocking agent Dibenamine on heart failure.[14, 15, 16] Their findings were similar to ours in that there was a decrease in peripheral resistance with the reduction of blood pressure and a transient increase in cardiac output. They concluded that in heart failure neurogenic reflexes increase the arteriolar and venous tone, and are the cause of numerous secondary effects. Halmágyi and his associates also have recently recorded similar observations and conclusions.[17]

Summary

1. The immediate effects of hypotensive doses of hexamethonium given to 19 patients with various types of heart disease in congestive failure were a fall in venous pressure in all patients exhibiting initial elevations; shortening of the circulation time and a decrease in heart rate in most cases; and frequent symptomatic improvement in the degree of dyspnea and orthopnea.

2. Right auricular, right ventricular and pulmonary arterial pressures also were reduced following hexamethonium in patients with congestive heart failure. An increase in cardiac output with a marked decrease in total peripheral resistance was observed in one cardiac patient in which such determinations were carried out.

3. It is suggested that hexamethonium, by reducing the total peripheral resistance and diverting blood volume to the peripheral vasculature, may interrupt the vicious cycle associated with congestive heart failure by, first, decreasing the work demand of the left ventricle and, second, reducing venous overloading of the right heart.

Sumario Español

Dosis hipotensas de hexamethonium fueron administradas intravenosamente a 19 pacientes con varias clases de enfermedades del corazón en decompensación. Mejoramiento clínico juzgado por los métodos usuales se observó en la mayoría de los casos. Las presiones intracardíacas y de la arteria pulmonar decrecieron paralelamente a la presión arterial, luego de la administración de hexamethonium en cuatro pacientes con enfermedad hipertensa del corazón con decompensación cardíaca. Se sugiere que el hexamethonium, mediante reducción de la resistencia periférica y mediante una redistributión del volumen de sangre puede interrumpir el ciclo vicioso de la decompensación cardíaca.

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Electrocardiographic Studies during Cardiac Surgery

By E. J. Jaruszewski, Commdr. U.S.N., H. K. Hellerstein, M.D., and H. Feil, M.D.

The electrocardiographic behavior of the heart was observed in 100 patients undergoing heart operations. Most of the arrhythmias were unrelated to the cardiac operative procedure, but as in other thoracic procedures, were related to hypoxia, level of anesthesia, vagal reflexes, and changes in blood pressure. T_A and S-T displacements occurred in all groups and were thought to be related to altered dynamics of the right auricle and ventricle. Prevention, recognition and control of disturbances of cardiac mechanism are discussed.

THERE are excellent observations[15-21] concerning cardiac mechanism during anesthesia and surgery but there are few[10-14] on the behavior of the heart during cardiac and cardiovascular surgery. The present report is a record of the behavior of the heart in four common types of surgical procedures: ligation or section of a patent ductus arteriosus,[1] resection of the aorta in coarctation,[2] increasing pulmonary artery blood flow in congenital cyanotic heart disease[3, 4, 5] and resection of pericardial scar in Pick's Disease.[6] The incidence and nature of operative complications are evaluated. Prevention and control of disturbances of cardiac mechanism are discussed.

Methods and Materials

This study is of 100 patients, operated upon by Dr. Claude S. Beck. Forty-five patients had section or ligation of a patent ductus arteriosus. Eight had surgical correction of coarctation of the aorta. Twenty had resection of pericardial scars due to chronic cardiac compression. Twenty-seven had operations designed to increase the pulmonary artery blood flow either by the Blalock-Taussig or by the Potts procedure. The age distribution is recorded in table 1.

In all cases a medical cardiologist was present throughout the operation. The observer took frequent records and, in addition, watched the electrocardiogram. Changes in the electrocardiogram were correlated with direct observation of the heart, level of the blood pressure and anesthesia, and the operative procedure. All of the patients had preoperative and postoperative electrocardiographic studies. The observations on the four groups of patients are discussed separately.

The preoperative medication was the same in all groups. This consisted of morphine or codeine and atropine. Congestive failure, if present, was treated. Auricular fibrillation or flutter, if present, was controlled by adequate digitalization. Anesthesia was induced by nitrous oxide or Vinethene in all patients except where cyclopropane was used. Ether was employed for maintenance of anesthesia. The Rand positive pressure respirator[23] was employed with intratracheal intubation in all patients.

Patent Ductus Arteriosus

This group consists of 45 patients who were operated for a patent ductus arteriosus. In 44 patients the ductus was either tied or sectioned. In one patient (with a pulmonic systolic murmur and thrill but no diastolic murmur), exploration did not reveal a patent ductus arteriosus.

Cardiovascular Status before Operation. Cardiac enlargement was noted in 27 of 45 cases and was more marked in patients over 15 years of age. Although signs of impaired cardiovascular reserve occurred in several patients in the older age group, digitalis medication was not prescribed for any reason before or after operation. In general, the cardiovascular status of this group of patients was better than that of the cyanotic group, and was comparable with the coarctation group.

Operative Procedure. In the earlier operations the ductus was isolated and doubly ligated. In the later operations, the ductus has been sectioned, and in several cases, an aneurysmal

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dilatation at the site of insertion into the aorta was resected and the aortic wall approximated by sutures. There were no deaths in this group.

Medication during Operation. Two patients received repeated doses of atropine during the operation, one because of frequent ventricular beats, and one for its effect on bronchial secretion. One patient received quinidine lactate, 0.30 Gm. intramuscularly, because of multiple premature ventricular beats which appeared when the chest wall was opened. Four patients received intravenous Cedilanid because of rapid supraventricular rhythms (one because of interference dissociation with a rapid ventricular rate at time of closure; one because of sinus tachycardia prior to administration of the anesthetic; one because of the occurrence of supraventricular tachycardia during dissection of the ductus; and one because of sinus tachycardia). This operation was shorter in duration than the others, averaging 170 minutes, and ranging from 80 to 305 minutes.

TABLE 1.—*Age Distribution*

Diagnosis	Number Cases	Age Range (Years)	Predominant Age (years)
Patent ductus arteriosus	45	2-35	Average 12
Coaretation of aorta	8	9-44	7 below 23
Chronic cardiac compression	20	11-59	Average 38
Congenital cyanotic heart disease	27	8-28	Average 17

Electrocardiographic Changes

Heart Rate. There was a definite trend for the heart rate to change during various stages of the operation. The average rate before the administration of anesthesia was 92 and increased to 129 after induction. A further increase to 139 was noted when the pleura was opened. During dissection of the ductus the average rate increased to 148 and remained in this range until closure of the chest. Surprisingly, no significant change occurred immediately when the ductus was occluded.

Electrical Position. The patients were in the right or semiright lateral posture. In 24 per cent, the heart became electrically more "vertical."

Mechanism. All of these patients had sinus mechanism before anesthesia and at the time of closure the mechanism was again a sinus rhythm in all, although disturbances of rhythm occurred during the operation. In 26 patients, sinus mechanism persisted throughout the entire operation.

Premature Beats. In nine patients premature beats were noted (20 per cent). As shown previously, anesthesia and incision of the chest wall are often accompanied by the appearance of premature beats. Likewise, in this group two patients had premature beats appear during induction of anesthesia, four when the chest wall or pleura was opened, and three when the ductus was being dissected or sectioned. One patient had both auricular and ventricular beats; one, nodal; one, auricular alone; and six, ventricular. The premature beats occurred singly, and not in runs as in the pericardiectomy group. The patients receiving cyclopropane induction showed no disturbance of mechanism.

Complex Rhythms. The following arrhythmias occurred in 13 patients: nodal rhythm, interference dissociation, supraventricular tachycardia, cardiac arrest, and ventricular tachycardia. Analysis of the time of their occurrence and relation to surgical procedures reveals that five occurred during induction; four when the chest was being opened; two when the ductus was being dissected; one when the ductus was being sectioned; and one when the operation was completed and the chest was being closed. In five patients the arrhythmia was intermittent and transient. In seven patients the arrhythmias persisted throughout the major part of the operation and throughout various phases. It is important to point out that premature beats and significant arrhythmias occurred more commonly *before* the cardiovascular part of the operation than *during* it. Similar arrhythmias have been observed during thoracotomies in general.

Cardiac arrest was encountered in a 7 year old boy and was successfully managed. While under ether anesthesia, the patient developed transient nodal rhythm with auricular pre-

mature beats, and spontaneously reverted to sinus rhythm when the chest was opened. Two hours and 25 minutes later, after the ductus had been sectioned, and while the clamp on the pulmonary end of the ductus was being released, sudden cardiac arrest occurred. The duration of the arrest, electrocardiographically recorded, was 75 seconds. The cessation of cardiac activity was recognized immediately. Manual cardiac massage and intracardiac epinephrine restored the heart beat. The following electrocardiographic changes were noted: sinus rhythm, nodal rhythm, auricular premature beats, cardiac arrest, ventricular tachycardia after massage and epinephrine, then interference dissociation for 10 minutes, followed by a short burst of ventricular tachycardia and finally reversion to sinus rhythm. The patient recovered without residual effects.

T_A and S-T Segment Changes. One of the most striking electrocardiographic changes noted in all cases of patent ductus arteriosus was the occurrence of depression of the T_A and the S-T segments. This depression occurred in all cases regardless of the level of these segments in the preoperative preanesthetic records. Thus, in 11 cases there was deviation in the preanesthetic records (S-T depression in leads II and III in seven cases, and in leads I and II in four cases). This preanesthetic depression was considered to be consistent with ventricular hypertrophy. Upon the induction of anesthesia, the depression of the S-T and T_A segments occurred in leads II, III and aV_F in 44 cases and in leads I and II in one case. Elevation of the T_A and S-T segments occurred in the right arm lead, as would be expected.

The degree of S-T depression increased during the operative procedure and showed definite trends. When the pleura was opened and the patient was put on an artificial respirator, the depression became more marked in 17 patients. While the chest wall was being closed, the depression decreased in three patients, became more marked in one, and in the remainder was unchanged. This depression was a transient phenomenon. In one patient it lasted four hours, but in every patient postoperative records showed regression of this finding.

The Influence of the Auricular T Wave on the Level of the S-T Segment. In the course of the above operations, the effect of the auricular T wave on the level of the S-T segment was clearly demonstrated. Since the auricular T wave may last 0.28 second or longer, it influences the level of the S-T segment. In three patients, there was conspicuous T_A and S-T depresson when the mechanism was a regular sinus rhythm. When middle nodal rhythm occurred transiently (no visible P waves), the S-T segment became isoelectric. Similar changes were noted in the cyanotic group (fig. 6). The depression of the T_A segment indicates an increased negativity of the auricular T wave. This occurs in other conditions in which there is an increased pressure in the atria, especially the right, as in cor pulmonale due to pulmonary fibrosis.

Changes in the QRS Complexes. Changes in electrical position have already been mentioned. The duration of the QRS complexes remained unchanged during the operation in all patients but one, who received quinidine sulfate intramuscularly during the operation because of ventricular premature beats. Electrical alternans of the QRS complexes was recorded in another patient. This developed immediately after ligation of the ductus and diminished gradually as the operation continued.

Coarctation of the Aorta (Eight Patients)

Condition of Cardiovascular System before Operation. Seven of the eight patients enjoyed excellent health, without restriction of physical activity. The oldest patient (age 44 years) had exertional dyspnea, occasional ankle edema, and severe throbbing headaches associated with hypertension in the upper extremities. Her physical condition improved with rest preoperatively. None of the patients required digitalis therapy.

These patients were excellent surgical risks from the cardiovascular standpoint. There was only slight to moderate ventricular hypertrophy as evidenced by changes in the electrocardiogram in two, and by roentgenographic examination in five. All had regular sinus rhythm. Intraventricular conduction was nor-

mal in seven, and of the Wolff-Parkinson-White configuration in one patient.

Operative Procedure. The patients were in a semiright lateral position. The coarctation was exposed and resected. In each patient it was possible to make an end-to-end anastomosis. In addition, one patient had a ductus arteriosus with a minute patent lumen, and the ductus was ligated and divided. There were no deaths.

TABLE 2.—*Electrocardiographic Changes during Anesthesia and Cardiac Surgery of 100 Patients*

	Coarctation of Aorta (8 cases)	Pericardiectomy (20 Cases)		Total Pericardiectomy Group	Congenital Cyanotic Heart Disease (27 cases)	Patent Ductus Arteriosus (45 cases)
		Sinus Mechanism (11 cases) % SM	Auricular Fibrillation or Flutter (9 cases) % AF			
No change in rhythm	(5) 62.5%	(2) 18.1%	(1) 11.1%	(3) 15%	(6) 22.2%	(26) 57.7%
Displaced Pacemaker*						
Under anesthesia before chest was opened	(1) 12.5%	(1) 9.09%	—		(8) 29.6%	(5) 11.1%
At one time or other during operation	(3) 37.5%	(4) 36.3%	—	(4) 20%	(14) 51.8%	(13) 28.8%
Premature Beats (excludes Ventricular Tachycardia)	(0) 0%	(5) 45.4%	(7) 77.7%	(12) 60%	(11) 40.7%	(9) 20.0%
Auricular Fibrillation	(0) 0%	(4) 36.3%	—	—	(1) 3.7%	(0) 0%
Ventricular Tachycardia	(0) 0%	(3) 27.2%	(3) 33.3%	(6) 30%	(3) 11.1%	(1) 2.2%
Ventricular Fibrillation	(0) 0%	(0) 0%	(1) 11.1%	(1) 5%	(1) 3.7%	(0) 0%
Cardiac Arrest	(0) 0%	(0) 0%	(0) 0%	(0) 0%	(6) 22.2%†	(1) 2.2%
PT_A and S-T segment Displacement						
Preoperative	(0) 0%	(2) 18.1%	(6) 66.7%‡	(8) 40%	(15) 55.6%	(11) 24.4%
Under anesthesia	(8) 100%	(6) 54.5%	(7) 77.8%	(13) 65%	(20) 74.1%	(45) 100%
Increased displacement when chest opened	(6) 75%	(3) 27.2%	(0) 0%	(3) 15%	(9 of 21) 42.8%	(13) 28.8%

* Includes A-V nodal rhythm, interference dissociation, but does not include supraventricular tachycardia, flutter, fibrillation or ventricular tachycardia.

† No arrests since the use of cyclopropane was discontinued.

‡ Refers to S-T depression only, since mechanism was auricular fibrillation.

Electrocardiographic Changes.

Extreme changes of rate, ectopic rhythms, premature beats, and changes in conduction were absent.

Rate. As expected, the rate was faster after induction of anesthesia, with an average increase of 30 beats per minute. Case 5 had sinus tachycardia (166) which remained around 150 throughout the operation. There were general trends in rate which apparently were related to the surgical procedures. When the pleura was entered the rate increased; when the clamps were applied above and below the narrowed aorta the rate slowed and the blood pressure in the brachial artery rose. When the clamps were removed and the anastomosis began to function, the rate increased and the blood pressure fell. The anticipated drop in blood pressure was controlled by intravenous administration of blood. At the close of operation, which lasted from four to nine hours, the heart rate averaged 140 beats per minute, 27 beats more than the rate during induction.

Mechanism. Preoperatively sinus rhythm was present in all cases. Sinus tachycardia was observed in all during the operation. In three patients the pacemaker shifted intermittently to the middle or upper A-V node throughout the operation. In one patient this occurred when clamps were applied to the aorta. This was the sole group in which premature beats were absent (table 2).

With the patient in the semiright lateral posture,[24] the electrical position of the heart

became more "vertical" in four and did not alter in four. In the latter four, two became electrically "vertical" when the left lung was packed down in order to effect exposure of the coarctation. During the rest of the procedure the position remained constant.

T_A and S-T Depression. After induction of anesthesia and before chest incision T_A and S-T depression in leads II and III appeared in every patient (fig. 1). Furthermore, this depression became more marked in six of eight patients when the pleura was entered. Some degree of T_A and S-T depression persisted throughout the operation, and was unrelated to the length of the operation. The postoperative records several days later showed that the T_A and S-T segments had returned to the isoelectric level.

Intraventricular Conduction. There was no change in the duration of intraventricular conduction. The patient with Wolff-Parkinson White complexes withstood surgery uneventfully.

Removal of Compression Scars of the Heart (20 Patients)

The records of 20 consecutive patients with constrictive pericarditis were reviewed. These patients were operated upon during the interval from 1944 to 1949. Since the first reports on the behavior of the heart during pericardial resection[11] considerable advance has been made in anesthesiology, and cardiac surgical technique. For this reason, a comparision of our results with those in the earlier series done by the same surgeon (Dr. C. S. Beck) is instructive of these advances.

Condition of Cardiovascular System before Operation. Clinically, these patients had a marked diminution of cardiovascular reserve, apparently due to cardiac compression alone in 18 of the 20 patients. In two patients rheumatic mitral valvular disease was present. These 20 patients had cardiac compression for relatively long periods of time (ranging from six months to two years in eight patients, three years in four patients, and five to 13 years in eight patients). Three patients had been subjected to multiple pericardiectomies previously. Eight patients were maintained on digitalis medication in the month preceding operation. Twelve received mercurial diuretics and/or abdominal paracenteses. There were eight patients with auricular fibrillation and one with auricular flutter. Digitalis was given to the patients with auricular fibrillation and to one case with regular sinus rhythm. Intraventricular conduction was less than 0.09 second, in all cases.

Operative Procedure. Operative details will be found in the publications of Beck.[25] The patient lay in a semiright lateral posture to provide an anterior approach.

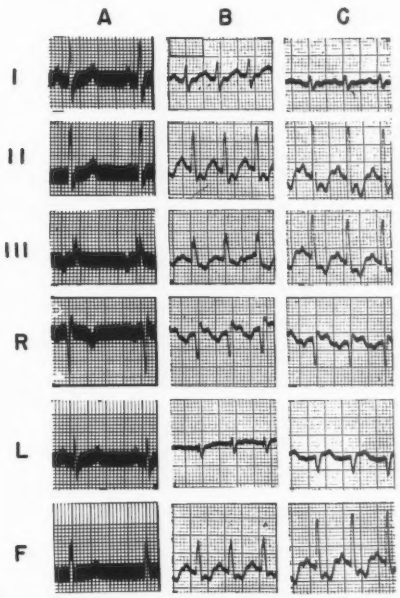

Fig. 1. Electrocardiograms of J. L. W., case 5, a 10 year old girl undergoing surgical correction of coarctation of the aorta. Records illustrate marked displacement of T_A and S-T segments under anesthesia (*B*), and increased displacement later during the procedure (*C*). *A* is the preoperative control record.

Medication during Operation. In contrast to the earlier experience, where routinely preoperative quinidine was given and where procaine was used topically (all directed toward reducing ectopic rhythms), in this series to only one patient (case 19) was quinidine (0.50 Gm.) given preoperatively. Furthermore, in only two patients (cases 8, 15) was it necessary to use a cardiotonic drug during the procedure.

The improved results are related to experience, technic and preoperative preparation. One patient (case 8) developed supraventricular tachycardia with a rate of 210 while the chest wall was being dissected. Within 10 minutes the rate slowed to 125 per minute, and interference dissociation appeared. Cedilanid* (0.8 mg.) was given intravenously, and the rate remained in the vicinity of 125. The mechanism at the end of the operation and for 17 days thereafter was auricular flutter. Reconversion was then effected by the use of quinidine. The other patient (case 15) had auricular flutter with a preoperative ventricular rate of 100 and had not been given digitalis. While under anesthesia, before surgical incision was made the patient developed a ventricular rate of 200 with obvious cardiac embarrassment. Cedilanid (1.6 mg.) was given intravenously, with slowing of the rate to 125 within five minutes. We now advise that all patients with auricular flutter or fibrillation receive preoperative digitalization to prevent the need of digitalization during the procedure.

Electrocardiographic Changes

Rate. The rate increased with the induction of anesthesia. The average rate was 90 (65–125) before induction, and after induction rose to 121 (75–200). This increase occurred approximately equally in patients with regular sinus rhythm and in those with auricular fibrillation. Unlike the other groups, opening the chest and the pleura was not accompanied by as marked a change of heart rate. About one-half of the cases had an acceleration of 10 beats or more when the chest was opened. The rate remained relatively stable during the process of dissection of the pericardium, except for spurts of short-lived tachycardias (to be discussed in detail later). At the close of the operation, which lasted from three to five hours, the average rate was 10 beats or more faster than the induction rate in 10 cases and unchanged or slower in the remaining ten. This is in contrast to the cases with coarctation who had a closing rate 27 beats faster than at induction. The longer duration of the latter operation (four to nine hours) may account for a greater terminal rate. Postoperative records of the patients with pericardiectomies showed a return of the average rate to 91 per minute.

Mechanism. Preoperatively, 11 patients had regular sinus rhythm, eight auricular fibrillation and one patient had auricular flutter. For convenience, the first group is designated as group A, and the patients with fibrillation or flutter as group B.

In table 3, the changes in mechanism during various parts of the operation are summarized. In group A during induction of anesthesia and opening of the pleura and pericardium, 4 of 11 patients developed supraventricular arrhythmias. Similar arrhythmias have been noted by Kurtz and co-workers during noncardiac operations.[16] However, during pericardial resection, there was a definite relationship between the manipulation of the heart, traction on the pericardium as it was being dissected free, and the appearance of ventricular premature beats, singly, in pairs, or in runs (ventricular tachycardia). (See figs. 2 and 3.)

During the periods of dissection (group A) auricular fibrillation of flutter was recorded in four patients and nodal rhythm in two patients, making a total of 6 of 11 patients (54.5 per cent) who developed supraventricular arrhythmias. At the time of closure, two patients still had auricular fibrillation or flutter.

The patients in group B with auricular fibrillation developed no significant arrhythmias prior to resection of the pericardium. During pericardial resection, the same relationship between manipulation and the appearance of ventricular tachycardia was also noted in group B.

In this series, one patient (case 14) developed ventricular fibrillation (fig. 3). While an invasive pericardial scar was being dissected from the myocardium ventricular fibrillation developed and persisted for five minutes. The nature of this arrhythmia was recognized immediately, electrocardiographically and by inspection. Within two to three minutes defibrillation was accomplished by the use of electric shock, manual massage and intracardiac adrenalin.[27]

* Generously supplied by Sandoz.

The immediate mechanism following defibrillation was idioventricular rhythm with a rate of 50 per minute, showing a marked delay of intraventricular conduction. Subsequently, this changed to auricular fibrillation with a rapid ventricular rate (190) with varying intraventricular conduction and finally to auricular fibrillation with normal intraventricular conduction. This patient, in retrospect, was the only one in this group whose preoperative electrocardiogram showed premature ventricular beats. Postoperatively, the premature ventricular beats (electrocardiographically of the same origin) persisted. The patient died 18 hours

TABLE 3.—*Changes of Cardiac Mechanism during Pericardiectomy*

Case No.	Preoperative	Under Anesthesia	Chest or Pleura opened	Pericardium entered	Dissection Pericardium	Finish Op. Closure	Postoperative	Comments
Group A								
1	RSR	RSR	RSR	ST	AF with RBBB VT × 2	RSR	RSR	AF with RBBB for 5 min. VT less than 1 min.
2	RSR	Nodal	ST	ST, occasional VPB	ST, paroxysms nodal	ST	RSR	Nodal rhythm occurred before surgical incision. Uneventful throughout
4	RSR	ST	ST	ST	ST	ST	RSR	
5	RSR	ST	ST	ST	RSR, occasional VPB	RSR		Sinus mechanism, occasional VPB
7	RSR	ST	ST	ST	ST, paroxysms VT, AF	ST	RSR	During dissection, paroxysms VT and transient AF
8	RSR	SVT	ID	ID	ID, A flut, VPB	A flut	A flut RSR	Cedilanid (0.8 mg.) during operation. A flut persisted 17 days. Converted with digitalis and quinnidine
10	RSR	ST	ST	ST	ST, occasional VPB	ST	ST	—
11	ST	ST	ID	A flut	A flut	AF	AF	AF permanent postoperative
12	RSR	ST	ST	ST	ST	ST	RSR	—
13	RSR	RSR	ST, rare VPB	Nodal	Nodal, ST, paroxysms VT, APB, VPB	ST	RSR	Periods of nodal rhythm Bursts of VT (12 sec., Many APB and VBP
18	RSR	ST	ST	ST	ST, paroxysm VT	ST	—	Paroxysm VT (9 sec.)
Group B								
3	AF	AF	AF	AF	AF, occasional VPB	AF	AF	Uneventful
6	AF	AF, occasional VPB	AF, many VPB	AF, many VPB	AF, bigeminy	AF, bigeminy	F, occasional VPB	Bigeminy from time of resection to closure
9	AF	AF, occasional VPB	AF	AF	AF, paroxysm VT, VPB	AF	AF	VT with multifocal VPB during dissection
14	AF, occasional VPB	AF	AF	AF	AF, *VF*, AF	AF, occasional VPB	AF, occasional VPB	Ventricular fibrillation (5 min.) electroshock, —AF
16	AF	AF	AF, occasional VPB	AF	AF, occasional VPB	AF	AF	—
17	AF	AF	AF	AF	AF, VPB, short VT	AF	AF	Bursts of VPB (really "brief" VT)
19	AF	AF	AF	AF	AF	AF	AF	Uneventful
20	AF	AF	AF	AF, occasional VPB	AF, short VT	AF	AF	Short runts of VT near end of dissection
15	A flut	A flut or SVT	AF	AF	AF, nodal	Nodal	RSR	Cedilanid (1.6 mg.) given during anesthesia because of rapid rate

Key

AF	Auricular Fibrillation	APB	Auricular Premature Beats
A flut	American Flutter	VT	Ventricular Tachycardia
RSR	Regular Sinus Rhythm	VF	Ventricular Fibrillation
ST	Sinus Tachycardia (more than 100)	SVT	Supraventricular Tachycardia
Nodal	Nodal Rhythm	ID	Interference Dissociation
VPB	Ventricular Premature Beats		

postoperatively because of a bronchopleural fistula.

Electrical Position of the Heart. The patients were in the supine position. Nine of the 20 patients showed no change in the electrical position of the heart during the entire procedure. This may be due to the relatively fixed anatomical position demonstrated preoperatively by roentgenographic and fluoroscopic studies. Four patients exhibited a change in the electrical position during anesthesia or when the pleura was opened. Of these, three became more vertical and one less vertical. In seven patients, the electrical position changed during pericardial resection and was related to manipulation of the heart. When the surgeon was dissecting the left lateral region of the pericardium, the electrical position became less vertical. When dissection was being accomplished on the right lateral region, the heart became more vertical. At the time of closure, the electrical position reverted to the original preoperative value.

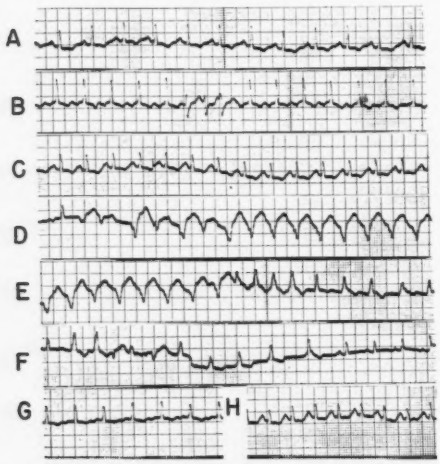

FIG. 2. Serial electrocardiograms of J. E., case 13, 11 year old girl undergoing pericardiectomy who developed paroxysmal ventricular tachycardia during resection of the pericardial scar. *A*. Time 10:20 a.m. Control record showing sinus mechanism (lead II). *B* and *C* are continuous records made at 10:25 while resection of scar was under way. There is a changing mechanism from nodal to sinus rhythm with a burst of three premature ventricular beats. *D*, *E*, and *F* are continuous records one minute later (10:26) showing transition of nodal rhythm to ventricular tachycardia and then sinus rhythm. When the ventricular tachycardia appeared a rest period was instituted and the lungs were inflated. *G*. Time 10:32. Operation was resumed. Nodal rhythm is present. *H*. Time 12:05. Record at end of operation showing sinus mechanism.

T_A and S-T Segment Changes. Six of 11 patients in group A developed T_A and S-T segment depression while under anesthesia (table 2). While under anesthesia, six patients in group B (four on digitalis and two without) showed depression or increased depression, respectively, in leads II and III. As in group A resection of the pericardium had surprisingly little effect on the ST-T complex. Only three cases showed significant changes. In two patients there was an increased depression in

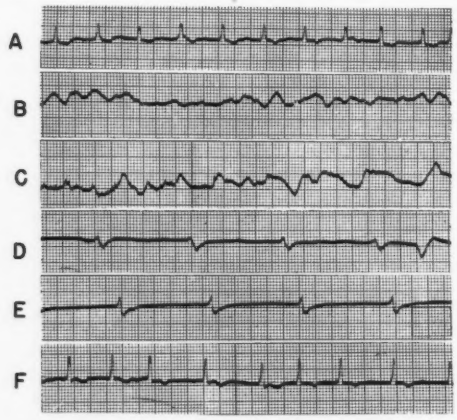

FIG. 3. Serial electrocardiograms of J. K., case 14, a 40 year old man undergoing pericardiectomy, demonstrating restoration of an effective cardiac mechanism following ventricular fibrillation. *A*. Time 9:00 a.m. Control record (lead II) showing auricular fibrillation with an average ventricular rate of 130. *B*. Time 11:00 a.m. Record shows ventricular fibrillation. While the invasive scar was being separated from the myocardium, the heart dilated acutely, became cyanotic, and ventricular fibrillation occurred. *C*. Time 11:05. One minute after the first electric shock. Ventricular fibrillation persists but some complexes are beginning to have form. *D*. Time 11:15. After the second shock and intracardiac adrenalin an idioventricular rhythm (rate 51) occurred with no visible or electrical evidence of auricular activity. An occasional premature ventricular beat is present *E*. Time 11:20. Idioventricular rhythm persists. At 11:25 auricular fibrillation with an average ventricular rate of 187 appeared. The operation was completed. *F*. 12:35 Time of closure. Auricular fibrillation persists.

leads II and III, while one patient showed marked elevation in lead I and depression in lead III, similar to the injury patterns observed in injury to the anterior wall of the myocardium. The changes in the last patient were transient, and were again transiently observed during a second pericardiectomy. At this time, the changes occurred when the distal end of the anterior descending coronary artery was nicked. Serial postoperative records revealed no evidence of a myocardial infarction. The S-T segment displacement and T-wave inversion which occurred postoperatively was considered to be due either to pericarditis or digitalis therapy.

Changes in the QRS complexes. In this series, the intraventricular conduction time was remarkably constant throughout the procedure. Of the entire group, only two cases had a temporary increase in conduction time. Case I developed right bundle branch block during a period of transient auricular fibrillation and case 14, following the episode of ventricular fibrillation, had a temporary prolongation of the intraventricular conduction time when the mechanism was restored to auricular fibrillation. Both of these patients had normal intraventricular conduction time at the end of the operation.

Amplitude of QRS Complexes. Low voltage of the QRS complexes is found commonly in constrictive pericarditis and is thought to be due to the shielding effect of fibrous pericardial scar and fluid. Since only 25 per cent of our patients had increase of amplitude postoperatively or at the time of discharge from the hospital, it is probable that the low voltage preoperatively is due to both shielding by the fibrous scar and the disuse atrophy of the myocardium.[28] Some of our patients showed delayed increase of voltage, some as late as one year *after* operation (fig. 4). This would imply that there had been an increase in the muscle mass and electrical potentials and is consistent with the concept that atrophy is reversible.[29]

Cyanotic Heart Disease with Deficient Pulmonary Circulation (27 Patients)

Twenty-four patients had the classic features of the tetralogy of Fallot, one had isolated dextrocardia with pulmonic stenosis, interventricular septal defect and dextroposition of the aorta; one had the pentalogy of the Cuban school (tetralogy of Fallot with an interatrial septal defect and left ventricular hypertrophy), and one patient had a probable truncus arteriosus.

Condition of Cardiovascular System before Operation. Clinically these patients had cyanosis and marked limitation of physical activity. The diminution of cardiovascular reserve was indicated by voluntary or imposed restriction of activity and exertional dyspnea. However, none of these patients had signs of congestive heart failure or were receiving digitalis Although surgical intervention is advocated for patients over 2 years of age,[30] in our series three patients below 2 years of age were operated upon because of serious underdevelopment and nutritional failure.

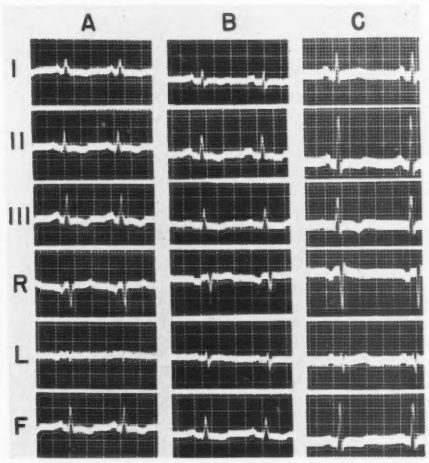

FIG. 4. Electrocardiograms of E. K., case 8, a 34 year old male, demonstrating delayed increase in voltage following pericardiectomy. *A*. Preoperative record. *B*. Seventeen days after operation *C*. Seventeen months later.

Operative Procedures. In 16 patients, a subclavian-pulmonary artery anastomosis[8] was performed, in eight patients an aortic-pulmonary anastomosis[4] and in thee patients exploratory thoracotomy alone was the procedure. In the last group, one patient had severe pulmonary stenosis with poststenotic aneurysmal dilatation of the left pulmonary artery. In

the other two patients a pulmonary artery could not be demonstrated at the time of operation. In each the aorta was extremely large.

Anesthesia. In the earlier part of this series, cyclopropane was used alone in nine cases, and together with ether in eight cases. In the last 10 cases of this series (and routinely in subsequent cases) ether was employed alone or supplemented by nitrous oxide or Vinethene induction. There were 10 deaths in the cyclopropane groups and none in the ether group. All six instances of cardiac arrest occurred in the cyclopropane group. The high incidence of cardiac complications in cyclopropane anesthesia has been noted by others.[16, 31–34] The

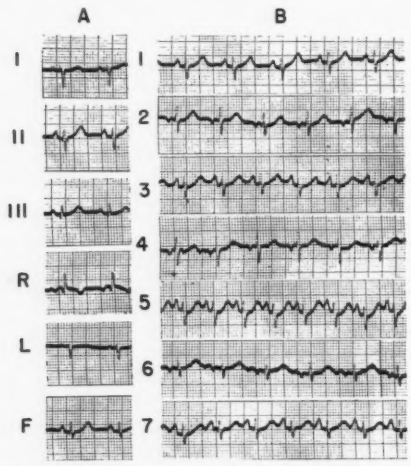

FIG. 5. Serial electrocardiograms of R. M. F., case 23, a 28 year old female with tetralogy of Fallot, showing frequent displacement of the pacemaker and the effect of intravenous atropine. Column *A*. Control record, under ether anesthesia. Column *B*. All lead II. Row 1, time 8:45 a.m. Under anesthesia. Sinus rhythm. Row 2, time 8:50. Skin incision has been made. Pacemaker displaced to the A-V node. Row 3, time 9:00. Sinus rhythm resumed spontaneously while the ribs were being resected. Row 4, time 9:50. The pleura has been entered. Again the pacemaker was displaced to the A-V node. Nodal rhythm persisted until the administration of intravenous atropine at 10:15. Row 5, time 10:18. Resumption of sinus mechanism after atropine. Row 6, time 11:45. While the anastomosis was being made, nodal rhythm again appeared, and the rate slowed from 150 to 94. Row 7, time 12:10. Because of the persistence of nodal rhythm, more atropine (0.4 mg.) was administered intravenously, and sinus mechanism was restored.

mortality rate of the last 10 cases was 10 per cent, and in the subsequent 30 cases, it has remained 10 per cent. The reduction is attributed to the use of ether, atropine, positive pressure respirator, rest periods, and experience of surgeon and anesthetists.

Medication during Operation. The need for repeated doses of atropine during the operation is demonstrated by the observation that cardiac arrest occurred on an average of three to four hours after the preoperative dose of atropine, when its effect had worn off. In six of the last 10 patients, repeated injections of atropine were given. There were no deaths. The indications for additional atropine consisted of the appearance of (1) nodal rhythm, (2) interference dissociation and (3) marked slowing of the sinus rate. These changes were usually related to the opening of the chest wall, retraction and dissection of the pulmonary artery, and retraction of the lungs (figs. 5, 6, 7 and 8). The response to intravenous atropine was immediate, with restoration of regular sinus rhythm and an acceleration of a previously slow rate.

Cardiac Arrest. As mentioned, there were six cases of cardiac arrest; one survived. Electrocardiographic changes before, during and after cardiac standstill are listed sequentially in table 4. In four patients, arrest occurred when the pulmonary artery or aorta was being dissected, or the anastomosis being made. In one patient, cardiac arrest occurred during the incision of the skin, and in another, after the chest had been entered and the lungs were being retracted. In these cases, cardiac arrest was probably produced by reflexes from the operative field, with inadequate protection by atropine administered several hours previously. In each instance sinus mechanism was restored, even though the period of recorded cardiac arrest varied from 33 seconds to five minutes. Three patients died within three hours after completion of operation, two within 24 hours, and one survived without residual effects.

Electrocardiographic Changes

In this group there were more disorders of the heart beat than in operations on patients with

noncyanotic congenital heart disease or constrictive pericarditis. In the latter group,

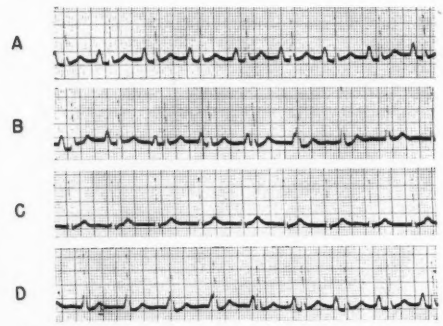

FIG. 6. Serial electrocardiograms of D. P., case 19, a 15 year old boy undergoing surgery for congenital cyanotic heart disease. The records illustrate the effect of the auricular T wave on the level of the S-T segment. *A* is the control record (lead aV_F) after induction of ether anesthesia, showing sinus mechanism with depression of the T_A and S-T segment. *B*, *C*, and *D* are continuous records. In *B* there is a gradual displacement of the pacemaker with the previously depressed S-T segment returning to an isoelectric level. In *C* nodal rhythm is present with isoelectric S-T segments. In *D* there is a gradual return of sinus mechanism. Because of the effect of the negative auricular T wave, the S-T segment again is depressed below the isoelectric level.

"extracardiac"—that is, on the great vessels. More likely alteration of pulmonary pressures incident to inhalation anesthesia and to compression of the lung or pulmonary artery in effecting the anastomosis would increase the right to left shunt and thus the degree of hypoxia.

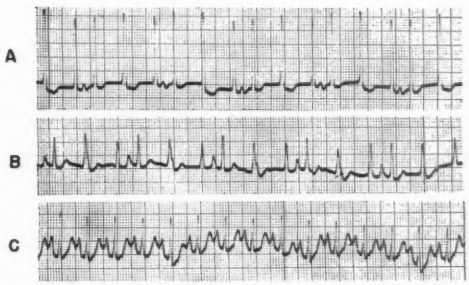

FIG. 7. Serial electrocardiograms of K. A. B., case 6, an 11 year old girl undergoing surgery for congenital cyanotic heart disease. Complex rhythms unrelated to the surgical procedure itself occurred. *A*. time 8:40 am. Control record (lead 2) under light anesthesia, showing complex arrhythmia, dissociaton by interference. *B*. Time 8:50. P waves are more prominent. There is a sinus rhythm with parasystolic foci. *C*. Time 1:10 p.m., an hour after completion of Potts operation. Sinus mechanism resumed spontaneously.

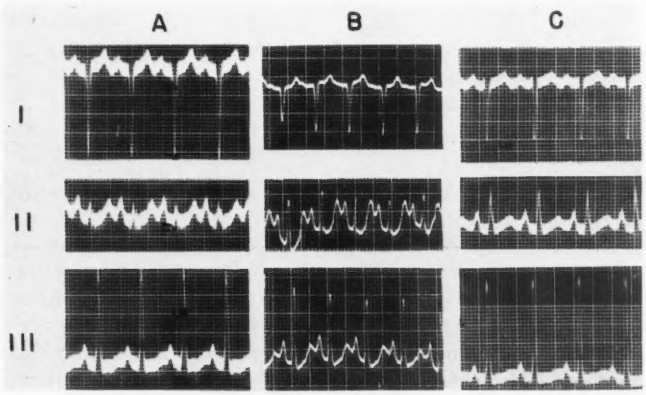

FIG. 8. Electrocardiograms of K. A. B., an 11 year old girl undergoing surgery for congenital cyanotic heart disease, illustrating the effect of anesthesia on the T_A and S-T segments, and the transient nature of the displacements. *A* is the preoperative control record. *B* shows marked T_A and S-T depression during ether anesthesia. *C*. Postoperative record showing minimal displacement.

changes in rhythm were due to cardiac manipulation. In the cyanotic group the disturbances were related to hypoxia and less to direct causes since the operations were essentially

Rate. The average preanesthetic heart rate was 116 per minute, which was higher than in the other (older) groups. After induction of anesthesia there was an increase to an averge rate

of 130. During the period between the opening of the pleura and dissection of the pulmonary and subclavian arteries and/or aorta, there was a further gradual increase to 140. The maximum average rate (151) occurred when the anastomosis was made. Upon closure of the chest, the rate decreased to an average of 141 per minute.

Mechanism. Preoperatively all patients had sinus rhythm. In addition to the six patients with cardiac arrest, the mechanisms during the operation were as follows: (a) six patients showed sinus rhythm alone, (b) six patients had sinus rhythm with auricular, nodal or ventricular premature beats, and/or short runs of ventricular tachycardia, (c) eight patients had sinus rhythm with periods of nodal rhythm, and (d) one patient had transient interference dissociation.

Premature beats were recorded in 9 of 21 patients; ventricular in six, auricular in two, and nodal in one. They occurred when the pleura was first entered in four cases, during the dissection of the great vessels in four cases, and at the time of anastomosis in two cases.

There was a similar tendency for nodal rhythm to occur more frequently during induction of anesthesia and incision of the chest wall (five cases) than during surgery of the great vessel (three cases). In only two of the eight patients, did nodal rhythm persist to the time of closure. Atropine was administered intravenously in four patients and restored the mechanism to a sinus rhythm. Interference dissociation likewise was transient, occurring during induction of anesthesia, and often spontaneously disappearing when the pleural space was entered. Apparently the appearance of nodal rhythm, interference dissociation and premature beats were causally related to the anesthetic more than the surgical cardiac procedure, since most occurred before the heart was manipulated.

T_A and S-T displacement. Displacement of the T_A and S-T segment was greater than in

TABLE 4.—*Sequence of Electrocardiographic Changes Preceding, During, and After Cardiac Standstill (Six Patients)*

Case 1. E. R.
Nodal tachycardia, cardiac arrest (complete standstill), multifocal ventricular beats, paroxysms of ventricular tachycardia with standstill, sinus tachycardia with right bundle branch block, sinus tachycardia with normal intraventricular conduction.

Case 2. J. Y.
Sinus tachycardia, sinus rhythm with delayed intraventricular conduction and prolonged P-R interval, sinus bradycardia, complete cardiac arrest (standstill), multifocal ventricular beats in bursts, idioventricular rhythms, rate 70, sinus tachycardia (150), sinus bradycardia with aberrant ventricular conduction, 3:2 S:A conduction, cardiac arrest, sinus tachycardia (150), delayed ventricular conduction, short paroxysms of ventricular tachycardia, electrical standstill, ventricular escapes, idioventricular rhythm sporadic, paroxysms of idioventricular beats, ventricular tachycardia, sinus tachycardia (150), cardiac standstill, coupled idioventricular beats, chaotic heart action, standstill, idioventricular isolated beats, standstill, idioventricular escapes, ventricular tachycardia in paroxysms, nodal rhythm, sinus rhythm with right bundle branch block, sinus rhythm with normal intraventricular conduction.

Case 3. P. R.
Nodal rhythm with frequent ventricular premature beats, auricular fibrillation with right bundle branch block, auricular standstill with ventricular escapes, complete cardiac standstill, ventricular escapes in pairs and threes, ventricular tachycardia, supraventricular tachycardia, sinus tachycardia.

Case 12. K. K.
Sinus tachycardia, ventricular tachycardia, cardiac arrest, sinus tachycardia.

Case 13. O. B.
Sinus tachycardia, cardiac arrest, sinus tachycardia.

Case 24. P. W.
Sinus tachycardia, interference dissociation, idioventricular rhythm with occasional sinus activity, cardiac standstill, ventricular escapes with irregular sinus activity and short periods of sinus recapture, sinus bradycardia (50), idioventricular rhythm with occasional conducted sinus beat, short bursts of sinus recapture, ventricular fibrillation.

the other groups (fig. 8). It occurred during the induction of anesthesia, and had a tendency to become more marked when the pleura was entered and the great vessels were isolated. Depression occurred in leads II, III, aV_F, and elevation in lead I and aV_R. In eight cases with depression of the S-T segment in preoperative records, additional S-T and T_A displacement occurred. Postoperatively, these displacements disappeared, again illustrating the evanescent nature of this charge. Postoperatively, ST-T changes of pericarditis occurred in three patients.

QRS Complexes. In three cases there was delay of right intraventricular conduction during the anastomosis.

Discussion

In the course of cardiac or noncardiac surgical procedures, a majority of patients will show some disorder of the heart beat.[15, 16, 19, 20] Such abnormalities (premature beats, tachycardia, displaced pacemakers) are usually transient and unaccompanied by clinical signs of embarrassment of the circulation. However, early recognition of significant arrhythmias and other electrocardiographic changes may forestall serious complications.

There were common features in all groups which were usually unrelated to the cardiac surgery, but were related to thoracotomy, anesthesia, hypoxia, and reflexes. These included changes in heart rate, electrocardiographic positional changes, displacement of the pacemaker, and T_A and S-T segment displacements.

A progressive increase of heart rate was noted in all four groups as the operation continued. The rate decreased at the end of the operation. This was true regardless of the type of anesthesia used.[36] In the younger patients the increase of heart rate was greater than in the older patients. In patients under 3 years of age, when the heart rate fell below 125, there was a decrease in blood pressure, and an increase of cyanosis. It is important to correlate the rate under anesthesia with the preanesthetic rate. The relative innocuousness of rates of 150 per minute in the young should be recognized. Therapy intended only to slow the heart rate, especially at the end of an operation, should be discouraged. In some of our younger patients, 6 to 12 hours have elapsed before the rate returned to lower levels.

Apprehension and fear before operation are occasionally responsible for sinus or supraventricular tachycardia. Mousel[37] has stressed the importance of preoperative reassurance of the patient.

Mechanism. In our series there was a frequent disturbance of the cardiac mechanism during induction or maintenance of light anesthesia, before the surgical procedure was begun. The most common was displacement of the pacemaker, that is, shift of the pacemaker within the sinoauricular node, nodal rhythm, or interference dissociation. This is in agreement with the reports of others.[15, 16, 19, 38, 39] We have noted also that at the end of surgery, with the lightening of anesthesia,[18, 40] nodal rhythms were fairly common.

That anesthetic agents themselves occasion the occurrence of premature beats is generally accepted in that they frequently occur prior to the initiation of surgical procedures. However, it has been difficult to determine whether the incidence of premature beats is related to the type of anesthetic agent. In the 80 patients (exclusive of the pericardiectomy group) the over-all incidence of premature beats was 25 per cent (20 cases). Although the number of patients who had cyclopropane anesthesia was relatively small (22 patients), there was no significant difference in the incidence of premature beats in the groups receiving cyclopropane and ether, 27.2 and 24.1 per cent, respectively. This is at variance with the observations of others.[31, 34] However, in the cyanotic group there was a significant increase in the number of premature beats regardless of the anesthetic used. Hypoxia or other factors are more important than the anesthetic agent in the production of premature beats.

Frequent ventricular premature beats or bursts of ventricular tachycardia are significant enough to warrant temporary interruption of the surgical procedure. This is especially true in pericardiectomy and more recently in mitral and pulmonic valvular surgery. Exclusive of the pericardiectomy group, we have

found that the occurrence of premature beats during anesthesia does not indicate that they are forerunners of ectopic rhythms. If premature beats are present preoperatively, they are more likely to be forerunners of ectopic rhythms (case 14).

Displacement of T_A and S-T Segments. A constant effect of inhalation anesthesia on the electrocardiogram was the downward displacement of the S-T segment in leads II, III, aV_F and the upward displacement in aV_R. In many instances there was an increase in the amplitude of the P wave. These changes were noted prior to any significant increase in heart rate and before the operation. There is good evidence that alterations of the cardiopulmonary dynamics may account for most of these changes, which suggest "strain" of the right auricle and right ventricle. Peripheral venous pressure, right atrial and right ventricular pressures have been shown to be elevated by inhalation anesthesia[41, 42] and by positive pressure, controlled or supported respiration.[43] Other procedures which increased the "strain" on the right heart included opening the pleura and packing down the lungs, and temporary occlusion of a pulmonary artery,[44] as during the Potts operation. Increased displacement of the T_A and S-T segments occurred at this time. Hypoxia may also account for these displacements. Lindgren and Ohnell[40] noted that depression of the S-T segment occurred during periods of hypoxia and that an increase of oxygen supply was generally followed by partial or complete return to isoelectric levels. Since acute hypoxia produces pulmonary hypertension,[45] the T_A and S-T changes may be due to the increased right heart "strain" secondary to hypoxia, or due to subendocardial ischemia.

Effects of the Surgical Procedure. The disturbances of cardiac mechanism in nonthoracic surgery[16, 17, 36, 37, 38] are similar but less frequent than in our series. Intrathoracic procedures affect cardiac behavior.[46] For example, the effects of reflex vagal stimulation were commonly noted during certain procedures in all groups. This occurred (1) when the pleura was entered, (2) ribs retracted, (3) the lungs packed away, (4) the hilar vessels dissected, and (5) during dissection in the proximity of the vagi. We have noted that each of the above procedures frequently resulted in sudden bradycardia, a fall of blood pressure, and displacement of the pacemaker or appearance of ventricular premature beats. In each instance the situation was corrected by intravenous atropine and reinflation of the lungs. As our experience increased, atropine was administered prophylactically in anticipation of the complications just referred to. It is important to be alert for predominant vagotonic effects throughout the surgical procedure and especially near the end of the operation. In many cases, we have noted a reflex vagal effect when the chest wall was being closed. Each time the rib cage was approximated by another suture, there was a sudden drop in pulse rate. Such changes in rate, actually signs of impending cardiac arrest, were readily abolished by atropine.

In the cyanotic patients, the surgical procedure had an especially important effect on cardiac behavior. Serious disturbances such as arrest were apt to occur when a pulmonary artery was partially occluded in order to effect an anastomosis. During this time there is a greater shunting of blood from the right to the left circulation, increasing the systemic hypoxia. Here hypoxia appears more important than vagal influence alone. The potentiation of vagal action or acetylcholine[47] by hypoxia may account for the high incidence of complications in this group.

The pericardiectomy group illustrates that manipulation, traction, and displacement of the heart were responsible for the appearance of premature beats and bursts of tachycardia. The greatest incidence of arrhythmias occurred when the lateral aspects of the pericardial scar were resected, necessitating rotation, angulation, and dislocation of the heart. Similarly, manipulation and traction encountered during mitral valvular surgery in our own and others' experience[51] invariably produces ectopic beats and frequently tachycardia.

The ideal anesthetic has not yet been attained for intrathoracic cardiovascular surgery. Cyclopropane and ether are most extensively used. Originally cyclopropane was heralded

as an ideal anesthetic for patients with heart disease because of the high concentration of oxygen administered with it. Actually, with modern technics, an equally high or higher concentration of oxygen can be administered with ether. Most observers[1, 2, 16, 31, 34] agree that there is a greater tendency for serious arrhythmias to occur under cyclopropane anesthesia. More recently,[33] cyclopropane anesthesia has been modified by the addition of ether, or continuous intravenous procaine. Furthermore, since vagal activity is not depressed by cyclopropane, atropine should be given in addition. The role of the vagus during cyclopropane anesthesia is demonstrated by the abolition and prevention of arrhythmias by large doses of atropine. In our series, most of the serious complications, such as cardiac arrest (a manifestation of excessive vagal activity), occurred under cyclopropane anesthesia. On the other hand ether causes depression of vagal activity and relative dominance of the sympathetic system[34] and appears safer, if properly administered.

In view of the divergent reports,[7, 48, 49, 50] equally enthusiastic and condemnatory, it would appear that the most important thing is the selection of the anesthetic with which the anesthetist is most familiar. The maintenance of oxygenation and the recognition of danger signs with cyclopropane, and the transfer to another anesthetic (ether) in such instances would constitute a reasonable compromise. Our own preference is ether.*

In considering the management of the patient during the operation, a routine technic for the constant observation of the state of the circulation should be emphasized. The direct writing electrocardiograph and more recently the cathode ray electrocardiograph provide continuous information on the cardiac mechanism. Direct observation of the heart is also valuable in advising therapy and in the timing of rest periods. The ear oximeter[35] facilitates the earlier detection of hypoxia, and should be used routinely. The ultimate purpose of these modern electronic adjuncts is to maintain the patient in a surgical anesthetic state, well oxygenated, protected from serious reflexes (atropine, procaine) and with a normal cardiac mechanism and blood pressure. Hypotension is preferably controlled by blood and saline, supplemented by pressor drugs when necessary. Since ventricular fibrillation or cardiac arrest may occur in spite of the above precautions, the operative team should be well-trained and equipped for restoration of the heart beat.[8, 9, 10, 13, 26]

* Recently a combination of procaine, nitrous oxide and Thipental was found satisfactory in mitral commissurotomy.[43]

Summary

The electrocardiographic behavior of the heart was observed in 100 patients during anesthesia and during cardiac operations.

Arrhythmias observed during cardiac operations are usually unrelated to the cardiac operative procedure, but are related to the type and level of anesthesia, hypoxia, and reflexes mediated through the vagus. The incidence of arrhythmias in surgery of the heart is about the same as that encountered in thoracic surgery in general. Ventricular fibrillation and cardiac standstill occurred in eight cases. Restoration of cardiac mechanism was affected in six with survival of two patients.

Displacement of the T_A and S-T segments occurred frequently in all groups, with depression in leads II, III, aV_F, and elevation in aV_R. These deviations are thought to be due to changes in the dynamics of the right side of the heart incident to anesthesia and to hypoxia.

There were few significant changes during anesthesia and operation for coarctation of the aorta and for patent ductus arteriosus. Ventricular premature beats, singly or in runs, were related to cardiac manipulation, traction, and resection of pericardial scars. More serious complications occurred in the congenital cyanotic group. The incidence of complications decreased since cyclopropane was replaced by ether.

Rest periods during the operation, reinflation of the lungs, and atropine are important in the prevention of serious complications. The recording and observation of continuous electrocardiograms should be supplemented by direct observation of the heart itself.

Sumario Español

El comportamiento electrocardiográfico del corazón se observó en 100 pacientes durante cirugía cardíaca. La mayoría de las arritmias no fueron relaccionadas al procedimiento operatorio cardíaco, pero, como en otros procedimientos toráxicos, se debieron a hipoxia, nivel anestético, reflejos vagales, y cambios en presión arterial. Desplazamientos de la T y ST ocurrieron en todos los grupos y se creyeron debidos a los cambios dinámicos alterados de la aurícula y ventrículo derecho. La prevención, reconocimiento y control de estos desordenes del mecanismo cardíaco se discuten.

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Supraventricular Tachycardia Complicating Surgical Procedures

A Study of the Contributing Causes, Course, and Treatment of this Complication in Fifty Patients

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Persistent postoperative supraventricular tachycardia, despite adequate therapy, is a bad prognostic sign, and cardiac failure due to, or associated with, arrhythmia responds poorly to treatment. Of the 12 patients (24 per cent) resistent to therapy, eight developed congestive heart failure, with five dying as a result. The preoperative, intraoperative and postoperative factors contributing to the causes of this complication are reviewed, and the therapy, course and end results are discussed.

THE OCCURRENCE of supraventricular tachycardia during and following surgical procedures is a relatively infrequent but dangerous complication. Several case reports emphasizing its importance following chest surgery have been published,[1–3] but little is known of the incidence and behavior of such arrhythmias in other types of surgery.[4, 5, 11] We have studied these arrhythmias as they developed during the operative and postoperative course of 50 patients (54 instances of arrhythmia) with particular reference to: (1) underlying and precipitating causes; (2) course of the arrhythmia, including its response to treatment; and (3) the influence of the complication upon the surgical outcome and subsequent cardiac status.

MATERIAL

The electrocardiograms taken at Memorial Center between Jan. 1, 1946 and Sept. 1, 1951, interpreted as showing the postoperative onset of supraventricular tachycardia, were reviewed; 54 instances of this electrocardiographic abnormality formed the basis of this study and included 15 patients with auricular fibrillation, six patients with auricular flutter, four with flutter-fibrillation, two with auricular tachycardia, six with nodal tachycardia and 12 in whom the rhythm was clearly supraventricular but the exact focus of origin unidentified, henceforth classified as a group as supraventricular tachycardia. Nine patients had multiple arrhythmias. Patients with sinus tachycardia or tachycardia due to auricular or ventricular premature contraction were excluded. Ventricular tachycardia was not encountered. The charts of these patients were reviewed, and the data classified according to the headings which precede each discussion.

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OBSERVATIONS

Incidence

Fifty patients developed supraventricular tachycardia during or within 18 days of operation. Four had second operations followed by recurrent arrhythmia, making a total of 54 instances of this complication. No instance of arrhythmia unconfirmed by electrocardiogram is included, although a number of these occurred during the period covered by this study. Hence, we cannot give the exact incidence of supraventricular tachycardia following operations done at Memorial Center, but it would appear to be well under 1 per cent, since approximately 28,000 operations were performed during this five and two-thirds year period. Thirty-one of the patients were males; 19 were female. Forty-eight were white, two were colored. The age range was from 15 to 78 years, with a mean of 62.1 years and a median of 63 years. Ninety per cent were 50 years or older, 70 per cent 60 years or more of age.

Concomitant Diseases

Of the 50 patients, 14 had generalized arteriosclerosis; seven were obese; two had diabetes mellitus; two, benign prostatic hypertrophy; two, latent syphilis; three, thyroid

adenomas of which two had once been toxic; three had emphysema; one, parkinsonism; and one was an alcoholic. Twenty patients exhibited no significant disease other than the surgical condition necessitating their hospital admission.

Preoperative Cardiac Status

Twenty-one patients (42 per cent) had no history or laboratory evidence of heart disease preoperatively. The most prevalent cardiovascular disease was essential hypertension, which was found in 19 patients (38 per cent). Arteriosclerotic heart disease was present in 10 patients (20 per cent); this was evidenced in seven (14 per cent) by a history of angina pectoris and in three (6 per cent) by a history of healed myocardial infarction. One patient had rheumatic heart disease (mitral stenosis); another had mild thyrotoxic heart disease and a third had noncyanotic congenital heart disease. Five patients (10 per cent) had had cardiac arrhythmias prior to their first operative procedure, although in two of these there was no other evidence of cardiac disease. All patients had normal sinus rhythm at the beginning of surgery, and none showed evidence of congestive failure.

Cardiac enlargement was found in nine patients (18 per cent), confirmed in seven by chest x-ray films. In 40 (80 per cent) of the remaining 41 patients the cardiac size was recorded as normal; in 38 of these this clinical impression was confirmed by x-ray films of the chest.

An estimate of each patient's preoperative functional capacity was made, and the results were classified according to the method of the New York Heart Association. Of the 50 patients, 27 (54 per cent) were in class I, 19 (38 per cent) in class II and the remaining four (8 per cent) in class III.

Preoperative Electrocardiographic Findings

Preoperative electrocardiograms were obtained from 42 of the patients. Thirteen (31 per cent) of these tracings showed myocardial disease with normal sinus rhythm; of the 13, three had ventricular premature contractions, and one had both ventricular and auricular premature contractions. Of the 29 tracings (69 per cent) showing no evidence of myocardial disease, three had ventricular premature contractions, one had auricular premature contractions, and one had both ventricular and auricular premature contractions. Thus, of the 42 preoperative electrocardiograms, six (14 per cent) showed ventricular premature contractions only, one (2 per cent) showed auricular premature contractions only, and two (4.7 per cent) showed both ventricular and auricular premature contractions, making the total incidence of premature contractions 21 per cent. In comparison, out of 100 random electrocardiograms taken preoperatively in our laboratory, eight showed ventricular premature contractions, and one showed auricular premature contractions, an incidence of 9 per cent.

Cardiac Medication

Medication for heart disease, per se, was given to nine patients prior to their first operation. Of this number, five received digitalis, one quinidine, two both quinidine and digitalis and one received procaine. Of the four patients suffering second attacks of postoperative cardiac arrhythmias, one received digitalis and one was given both digitalis and quinidine prior to the second operation. Forty-one patients received no specific cardiac therapy preoperatively.

Operative Data

Of the 54 operations, 45 were major, averaging 3.6 hours in duration. The remaining nine were minor in the sense that the surgical procedure lasted less than one hour. Fifty-three of the 54 surgical procedures were done under anesthesia. Three patients (5.6 per cent) received ether, 21 (40 per cent) ether with induction by nitrous oxide, five (9 per cent) Pentothal alone, seven (13 per cent) Pentothal and local combined, six (11 per cent) Pentothal plus inhalation anesthesia, seven (13 per cent) spinal and four (7.5 per cent) local anesthesia.

The regional distribution of these operations was as follows: head and neck, nine (17 per cent); chest, 20 (37 per cent); abdomen, 14 (26 per cent); pelvis, five (9 per cent); extrem-

ities, including breast, six (11 per cent). Although operations on the chest constituted only 5 per cent of the operations performed, 50 per cent of the postoperative cardiac arrhythmias followed chest operations. The abdomen was the site of 15 per cent of the operations, with 18 per cent of the arrhythmias occurring in these patients; 22 per cent of the operations were in the head and neck region, with an 18 per cent incidence of arrhythmia; 20 per cent were in the pelvis with no incidence of abnormal rhythm; 38 per cent were in the extremities, including the breast, with a 14 per cent incidence of arrhythmia.

Sixteen (29.8 per cent) of the 54 surgical procedures were essentially uncomplicated, and six of these did not even have minor fluctuations in blood pressure and pulse. The average blood pressure fall of the remaining 48 (88.8 per cent) was 47 mm. Hg systolic and 25 mm. diastolic. The systolic blood pressure fell below 100 mm. Hg in 33 instances (63 per cent), and in 20 of these the duration of hypotension was longer than 15 minutes.

Cardiac arrhythmias developed during the operation in 11 instances (20.3 per cent). Five of these had received preoperative cardiac medication consisting of quinidine in two, digitalis in two, and Pronestyl in one. In one instance the abnormal rhythm subsided before completion of the operation. Cessation of the operation was required in two patients, the arrhythmia being associated with temporary cardiac arrest in one and with generalized convulsions in the other. Nine of these 11 patients had preoperative evidence of heart disease. The arrhythmia appeared to be precipitated by laryngoscopy in two instances, by gastric intubation and cardiac arrest in one each. In one patient the arrhythmia was just noted after a generalized convulsion and in the second it developed after pulmonary edema was established. In five instances, no apparent precipitating cause could be ascertained.

During the operation trauma to the heart and its environs was obviously associated with the onset of the arrhythmia in only three instances. Other fairly clear-cut etiologic events followed by rapid onset of arrhythmia included myocardial infarction in three patients, congestive heart failure in three, hypotension in three, pericarditis in two, cardiac arrest in one, pulmonary edema in one and digitalis toxicity in two. Less definite but possible causes were mediastinal shift in eight patients, pulmonary infarcts in three, extensive atelectasis in three, bronchopneumonia in two, mediastinitis in two, bronchial stump leak in one and spontaneous pneumothorax in one. Incidental and less clearly associated complications included: abdominal distention, five; terminal cachexia, four; lower nephron nephrosis, two; peritonitis, two; septicemia, one; and transfusion reaction, one.

Miscellaneous Factors

The average oral temperature of the 43 patients who were febrile at the onset of arrhythmia was 102 F., with a range of 99 to 104 F. Seven patients were afebrile. The hemoglobin level within 24 hours of the occurrence of arrhythmia was below 12 Gm. per 100 cc. in 11 patients, 12 to 17 Gm. per 100 cc. in 34 patients and above 17 Gm. per 100 cc. in three; this datum was not available in two patients. In four patients no predisposing cardiac disease nor any operative or postoperative complication could be found to account for the occurrence of the tachycardia.

Course of Arrhythmias

Onset and Duration

In table 1 the arrhythmias are tabulated according to time of onset and total duration. In 11 patients (20 per cent) the onset was intraoperative and in 43 (80 per cent) the abnormal rhythm developed within 6 hours to 18 days postoperatively. The median time was three days, the average 4.9 days. It is noteworthy that in 45 per cent the onset of the arrhythmia was observed to occur after the second postoperative day. Abnormal rhythm persisted for over five days in 16 instances (30 per cent), for one to five days in 14 (27 per cent), and terminated within 24 hours in the remaining 24 (43 per cent). It is our custom to try carotid sinus pressure and compression of the eyeballs prior to giving any drug therapy to patients with supraventricular tachycardia.

Fifty-three of the 54 instances of arrhythmia

were treated with specific cardiac drugs. In 42 (78 per cent) reversion to normal sinus rhythm was observed; however, the arrhythmia recurred in 14 of these. In 12 patients (22 per cent) the arrhythmia was refractory to therapy, and in six of these patients it was a major cause of death.

Treatment

Digitalis. Adequate doses of a cardiac glycoside were used in the treatment of 42 of the arrhythmias. In 25 patients it was the only specific drug given; control of the arrhythmia with reversion to normal sinus rhythm was observed in 18 instances. Sixteen patients were given both digitalis and quinidine with reversion of the arrhythmia in 13; in four of these patients digitalis alone, rather than the small doses of quinidine employed, appeared to be responsible for the reversion. One of these patients receiving other specific drugs (procaine, acetylcholine and Pronestyl) did not revert to normal sinus rhythm until digitalis was given. Thus, of the 42 patients given cardiac glycosides, 22 were apparently controlled primarily by the glycoside. Of the remaining 20, 10 were controlled as a result of the administration of quinidine or other specific treatment than digitalis. In the other 10 patients, the arrhythmia was never brought under prolonged control, although five reverted to normal sinus rhythm transiently. Three of these received other specific medications in addition to digitalis.

Digitalis was given intravenously to 22 patients, 20 receiving lanatoside C and two digitoxin. Of the 11 given the full digitalizing dose at once, three established normal sinus rhythm in less than 12 hours; three within 12 to 48 hours; two took 48 hours or more and in three the arrhythmia persisted. When the glycoside was given intravenously in divided doses over a 12-hour period to 11 patients, normal sinus rhythm was established in less than 12 hours after completion of digitalization in three instances, within 12 to 48 hours in five, in more than 48 hours in one, and in two the arrhythmia remained uncontrolled.

Digitalization was effected by intramuscular administration in nine patients, five of whom were given digitoxin, three Digalen and one lanatoside C. Of the three given the full digitalizing dose in the first injection, one reverted to normal sinus rhythm within 12 to 48 hours, one in 48 hours, and in one the arrhythmia persisted. One patient given intramuscular digitoxin in three 0.4 mg. injections over a 10-hour period reverted to normal sinus rhythm after the last dose. In five patients digitalization was spread over a 12 to 24 hour period; in two of these normal sinus rhythm was established 12 to 48 hours later; in two the arrhythmia disappeared more than 48 hours later, and one remained arrhythmic.

TABLE 1.—*Time of Onset and Duration of 54 Instances of Cardiac Arrhythmias*

	Time of Onset (Number of Cases)	Duration (Number of Cases)
Intraoperatively	11	
Postoperatively		
1 Hour		1
6 Hours	6	3
12 Hours		5
1 Day		15
2 Days	13	6
3 Days	5	3
4 Days	3	4
5 Days	4	1
>5 Days	12	4
Uncontrolled		12
Totals	54	54

The glycoside was given by mouth in 11 instances, 10 receiving 1.2 mg. or more of digitoxin and one 1.5 Gm. of digitalis leaf. Of the three given the full dose immediately, one established normal sinus rhythm within 12 hours, another in two days, and in the third the abnormal rhythm persisted. Four were digitalized over a 1 to 12-hour period with reversion to normal sinus rhythm within 12 hours after digitalization in one patient, in 12 to 48 hours in one, in 10 days in another; in the fourth the arrhythmia persisted. Four were digitalized slowly over a 12 to 36-hour period, one reverting 24 hours after full digitalization, two in two and five days respectively, and one remaining arrhythmic.

Thirteen patients developed congestive heart

failure: three before and 10 after the onset of arrhythmia. Ten were given a cardiac glycoside, all in adequate dosage. In four of these the heart failure cleared. In two the heart failure had cleared before the establishment of normal sinus rhythm; in one the heart failure disappeared rapidly after cessation of the arrhythmia. One patient manifested signs of congestive heart failure for six days after reversion to normal sinus rhythm. Two patients had persistent evidence of congestive heart failure despite adequate digitalization and control of their arrhythmia. Four patients were apparently unaffected by the administration of digitalis, both the arrhythmia and the congestive heart failure persisting until death. Three patients with congestive heart failure were not given digitalis; all died 3 to 12 weeks postoperatively with the persistent arrhythmia and heart failure being the major cause of death.

Four of the 42 patients receiving a digitalis preparation were intoxicated by the drug; two of these developed an arrhythmia concomitant with the intoxication. One patient who had been completely digitalized one week previously was mistakenly given 6 cat units of folia digitalis within four days and developed supraventricular tachycardia during the ensuing period of nausea and vomiting. Through error, another patient was given 10 mg. of digitoxin instead of 1 mg. and six hours later developed auricular fibrillation. Both of these arrhythmias reverted promptly when digitalis was stopped and quinidine given.

Quinidine. Following the onset of arrhythmia in 22 patients a quinidine preparation, most frequently quinidine sulfate, was administered. The intramuscular route was used in one patient to whom a total of 0.6 Gm. was given with reversion of the arrhythmia within 12 hours after the institution of therapy. Quinidine was given by mouth to 21 patients, 11 of whom simultaneously received other cardiac drugs. Normal sinus rhythm appeared in 15, and quinidine was felt to be primarily responsible for the reversion. Dosage varied from 0.4 to 18.0 Gm. given over a period of from eight hours to 11 days. The average dose was 3.9 Gm. given over an average time of 50 hours. In most patients the dose of quinidine was less than optimal, and no instance of cinchonism was encountered.

Eight patients with arrhythmia were treated with quinidine alone; two reverted to normal sinus rhythm within 12 to 24 hours, three within 24 to 48 hours, and in three instances the arrhythmia persisted. Seven patients who had been treated with digitalis glycosides without reversion developed normal sinus rhythm when quinidine was given, four in 12 to 24 hours, two within 24 to 48 hours, one requiring four days. There were five instances in which the administration both of quinidine and of digitalis failed to control the abnormal rhythm. Maintenance doses of quinidine ranging from 0.2 Gm. to 1.6 Gm. per 24 hours were given to 13 patients, but the arrhythmia recurred in four instances; the maintenance dosages of quinidine in these four patients were 0.9 Gm., 1.2 Gm., 1.2 Gm. and 1.6 Gm. per 24 hours. Four of nine patients not getting maintenance doses of quinidine had recurrence of arrhythmia.

Other Therapy

Vagal stimulation by means of ocular or carotid sinus pressure was recorded as having been tried in six patients, with a transient response in one; subsequently cardiac drug therapy accomplished reversion of the arrhythmia in all six.

Two patients received procaine intravenously (0.5 Gm.). In one, auricular tachycardia reverted to sinus rhythm within four hours; in the other auricular flutter persisted. Two patients received procaine amide. One with auricular tachycardia was unaffected by 0.5 Gm. intravenously; one with multiple arrhythmias reverted within three days, during which he received a total of 3.5 Gm. orally. Two patients received Prostigmin subcutaneously, and one with nodal tachycardia reverted within two hours after the administration of 1.0 mg. but the arrhythmia recurred three days later and did not respond subsequently to 0.5 mg. The other, a patient with auricular tachycardia, received 0.5 mg. twice without definite response. Three patients were given acetylcholine intravenously, and one with supraventricular

tachycardia reverted immediately after having received 20 mg.; one instance of auricular tachycardia and one of auricular flutter did not respond respectively to 10, 20, 30 or 40 mg. doses given separately over a 12 hour period.

Uncontrolled Arrhythmias

Of the 12 uncontrolled arrhythmias four were multiple types, three were auricular fibrillation, three were nodal tachycardia and two were unidentified supraventricular tachycardias. Some of the factors apparently contributing to persistent arrhythmia include organic heart disease noted preoperatively (10 patients), postoperative extracardiac complications with stormy course (six patients), preceding postoperative myocardial infarction and heart failure (four patients), and probably inadequate cardiac drug therapy (eight patients). Eight of these 12 patients developed heart failure; in two its onset preceded the arrhythmia. Four died primarily of heart failure; five died of infection, one of malignancy and one of cardiac arrest. Of the three patients with auricular fibrillation, two were receiving 0.2 mg. of digitoxin daily; the ventricular rate of one was consistently above 100 per minute while that of the other was below 100 per minute. In seven of the nine patients with other types of arrhythmias the heart rates were faster than 100 per minute terminally. In the remaining two patients these data were not recorded.

End Results

Twenty of the 50 patients were living at the time of last follow-up; the duration of this period postoperatively ranged up to 38 months, with an average of 12 months. None of these patients showed evidence of cardiac arrhythmia or of heart failure. Eight were maintained on digitoxin, and none was taking quinidine.

Thirty of the 50 patients have died, all within two years postoperatively, with an average postoperative survival of five and two-tenths months. At the time of death, nine had no evidence of cardiac failure or arrhythmia; four had the arrhythmia only; two had heart failure with normal rhythm; 11 had heart failure and arrhythmia. The cardiac status of four patients at the time of death was unknown. Ten patients were taking digitoxin. Nine of the 30 deaths were due to cardiac disease; persistent cardiac arrhythmia with ensuing heart failure was the major factor in the death of six of these; of the remaining three, two died of myocardial infarction and one of cardiac arrest. Six deaths were due to malignancies, six to infection, four to pulmonary infarctions and the other five to various extracardiac diseases.

Discussion

Although it is difficult to anticipate which patients will develop cardiac arrhythmias as a complication of surgery, 79 per cent of our patients had preoperative evidence of heart disease and/or clinically evident auricular or ventricular premature contractions. Preventive measures should include preoperative control of the extrasystoles supplemented by the use of digitalis when indicated.

Intraoperative systolic hypotension to 100 mm. Hg or less and postoperative cardiopulmonary complications appeared to be causally related to the onset of the arrhythmias. Anemia, fever, and parenteral administration of fluids or blood did not seem to be contributory. Combinations of these and other factors listed elsewhere appeared to be operative as suggested by the fact that 45 per cent of the arrhythmias developed after the second postoperative day.

Twenty per cent of the abnormal rhythms had their onset during the operation; trauma to the heart or to related autonomically innervated structures, cardiac arrest and pulmonary edema were possible precipitating causes in 5 of the 11 instances. The type of anesthesia given did not appear to be of import etiologically, but a significant fall in systolic blood pressure to less than 100 mm. Hg was noted in 63 per cent. The possible importance of hypoxia or anoxia could not be evaluated.

In the present study the cardiac arrhythmias responded slowly to therapy probably because of the serious organic disease responsible for their etiology. Vagal stimulation was almost wholly ineffective, while cardiac therapy was

only moderately successful. Of the 22 instances of arrhythmias thought to have been reverted by digitalis action, only eight occurred within 12 hours following the administration of the full digitalizing dose. Of the nine instances of arrhythmias thought to have been reverted by quinidine action, only three reverted within 12 hours following institution of therapy, but perhaps this can be explained in part by the cautious dosage schedules.[10]

Prompt attention to possible precipitating causes such as infarction, heart failure, fluid and electrolyte imbalance, and pulmonary and renal complications is demanded in addition to specific therapy. We recommend prompt digitalization, intravenously by preference: give 1.6 mg. of lanatoside C within a period of five minutes to patients who are not receiving maintenance doses of digitalis; follow the initial digitalizing dose by 0.2 mg. of digitoxin daily and change the daily amount according to accepted standards. If the arrhythmia persists for 48 hours quinidine is given in dosages of 0.4 to 0.6 Gm. every three hours until the arrhythmia reverts or toxicity develops. Although procaine and procaine amide are considered to be relatively ineffective in supraventricular tachycardia,[6, 7, 12] it is desirable to employ them when digitalis and/or quinidine have proven ineffective.[8, 9] Should the irregularity persist after 48 hours of quinidine and digitalis therapy, an infusion of 1,000 cc. of procaine, 0.1 per cent in 5 per cent glucose, is started and continued at a rate of 50 to 70 drops per minute until normal sinus rhythm is established. Instead of procaine, procaine amide may be given intravenously at the rate of 200 mg. per minute up to 1 Gm. total, or until arrhythmia ceases. With such measures, 80 to 90 per cent of these arrhythmias may revert to normal sinus rhythm. Both digitalis and quinidine should then be continued until the patient is fully ambulatory or longer if there are other indications for continued therapy. The patient who is taking maintenance digitalis when paroxysmal tachycardia develops is treated at once with quinidine and/or other medications as described above.

In the series reported here, supraventricular tachycardia resulted in little or no damage to the 38 patients who responded favorably to therapy, but the 12 patients in whom the abnormal rhythm could not be controlled survived an average time of only 3.6 months. Six died of heart failure, all within five months, and in seven others the cardiac complication contributed to death. The heart failure associated with uncontrollable arrhythmia was also usually refractive to treatment, and of eight such patients six died of congestive heart failure. Had the treatment of the arrhythmia and of the heart failure been more intensive, as above recommended, a few of the eight patients who were inadequately treated might reasonably have been expected to respond more favorably.

Summary and Conclusions

1. Fifty-four instances of cardiac arrhythmia developed as an operative or postoperative complication among 28,000 operations done at Memorial Center from 1946 to 1951.

2. All of the arrhythmias were supraventricular in origin and consisted of 15 instances of auricular fibrillation, 12 of unidentified supraventricular disturbance, nine of multiple arrhythmias, six of auricular flutter, six of nodal tachycardia, four of flutter-fibrillation, and two were auricular tachycardia.

3. Operations in the thorax were most frequently complicated by arrhythmias (20 instances), with operations in the abdomen (14 instances), and head and neck (13 instances) next in frequency.

4. In 42 per cent of patients cardiac disease was not detected preoperatively.

5. Hypertensive cardiovascular disease was present preoperatively in 38 per cent of the series, arteriosclerotic heart disease in 20 per cent, with cardiac enlargement being noted in only 18 per cent. By New York Heart Association criteria 54 per cent were class I, 38 per cent class II and 8 per cent class III.

6. Abnormal electrocardiograms were found preoperatively in 31 per cent, premature contractions in an additional 10 per cent.

7. The presence of auricular or ventricular premature contractions preoperatively justifies the preoperative control of these irregularities with quinidine or procaine amide.

8. The arrhythmia developed at operation in 20 per cent, postoperatively in 80 per cent,

with a median time of onset of three days. Forty-five per cent developed two or more days postoperatively.

9. A blood pressure fall to 100 mm. Hg or less, operative manipulation, temporary cardiac arrest and pulmonary edema were probably causes of the cardiac irregularities noted during surgery.

10. Postoperative pulmonary infarcts, infection, hypotension, pneumothorax, digitalis toxicity, fever, abdominal distention, cachexia and lower nephron nephrosis appeared to play a part in precipitating the arrhythmia postoperatively. Four patients had no discernible precipitating cause.

11. Cardiac glycosides were apparently effective in establishing normal sinus rhythm in 40 per cent of the arrhythmias, quinidine in 15 per cent, and miscellaneous measures in 22 per cent; 23 per cent of the arrhythmias were uncontrolled by any measure.

12. The average duration of the cardiac irregularity before normal sinus rhythm was established was 30 hours; these patients showed no apparent permanent damage from the arrhythmia.

13. Of the 12 patients in whom the arrhythmia was uncontrolled, 10 showed evidence of heart disease preoperatively. Eight of these patients developed congestive heart failure, five dying as a result. Persistent arrhythmia despite adequate treatment is a bad prognostic sign and cardiac failure due to or associated with arrhythmia responds poorly to treatment.

14. The prompt administration of digitalis and/or quinidine to patients developing supraventricular tachycardia preoperatively is recommended. Persistent failure to revert to normal sinus rhythm justifies a trial of procaine, procaine amide, and possibly acetylcholine or Mecholyl.

15. Twenty patients are living and well without any evidence of heart disease 4 to 38 months (averaging 12 months) after the onset of their arrhythmia.

16. Thirty patients are dead, nine dying of heart disease, six of recurrent cancer, six of infections, four of pulmonary infarcts and five of other diseases.

Sumario Español

Taquicardia supraventricular postoperatoria persistente no obstante tratamiento adequado es un signo de pronóstico malo y decompensación cardíaca debida o asociada con la arritmia responde pobremente a tratamiento. De los 12 pacientes (24 por ciente) no respondieron a tratamiento, ocho desarrollaron decompensación cardíaca, cinco muriendo como resultado. Los factores preoperatorios, intraoperatorios y postoperatorios que contribuyen como causa a esta complicación se revisan, y la terapia, curso y resultados se discuten.

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Electrocardiographic Findings in Cardiac Amyloidosis

By ALBERT J. JOSSELSON, M.D., AND RAYMOND D. PRUITT, M.D.

The electrocardiographic findings we analyzed in 15 patients found at the time of necropsy to have deposits of amyloid in the heart. Although 12 of the 15 tracings were regarded as abnormal, changes which could be held to be specific to cardiac amyloidosis have not been defined. The most common alterations encountered were auricular fibrillation, QRS complexes and T waves of low amplitude in the standard limb leads, and impaired auriculoventricular conduction.

DEPOSITS of amyloid may be found in the hearts of individuals afflicted with primary systemic amyloidosis, with amyloidosis complicating multiple myeloma and with secondary amyloidosis. An entity exists, also, in which the heart alone is infiltrated by amyloid. The descriptive phrase, "amyloid localized to the heart," has been applied to this condition.[1] The amount of amyloid deposited in the myocardium under this latter circumstance may be as extensive as in cases of primary systemic amyloidosis or the quantities may be functionally insignificant.

In another study,[2] detailed consideration has been given to the clinical and pathologic findings in a series of 29 cases in which amyloid deposits were found in the heart at necropsy. The object of this presentation is to record the electrocardiographic findings as they were available in this series of cases.

Fifteen sets of electrocardiograms have been studied. Ten were obtained from the series of 29 cases just mentioned in which deposits of amyloid were localized to the heart. Four were obtained from cases in which primary systemic amyloidosis was present and one was taken from a case in which amyloid disease complicated multiple myeloma.

The degree of cardiac amyloidosis in these 15 cases is summarized in table 1.

While mild atherosclerosis of the coronary vessels was a commonly associated finding in these 15 cases, in none was it of such extent as to be regarded as clinically significant. Congestive cardiac failure was the primary or contributory cause of death in 7 of the 15 cases.

The electrocardiograms in these 15 cases are reproduced in figures 1 to 4. An attempt has been made to assemble in each figure a group of tracings that have one or more features in common.

Figure 1 includes three tracings. In one of these cases (A-5),* the disturbance may be placed in the category of right bundle branch block. In lead V_1, the form of the primary ventricular deflection is of a qR type rather than of the RSR′ configuration encountered more commonly in right bundle branch block. The other two electrocardiograms in this figure are perhaps the most unique in the entire series. In both, a qR type of complex is present in lead aV_R, as commonly occurs in right bundle branch block, but in neither does the form of the primary ventricular deflection in lead V_1 support the presence of such a defect in conduction.

The electrocardiograms from six patients are reproduced in figure 2. Auricular fibrillation was present in each instance. The QRS complexes in the standard limb leads share the quality of low amplitude. The primary ventricular deflection in precordial lead V_5 is of an rs or Rs type.

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* The case numbers used herein correspond with those appearing in a study pertaining to the pathologic findings in cases of amyloid localized to the heart.[1]

In figure 3, another instance (case 5) of auricular fibrillation is included. Only standard limb leads were recorded and from these limited tracings the presence of a left bundle branch block may be suspected but not established. The other two cases are characterized by the presence of complete auriculoventricular dissociation. In case A-3, the focus in which ventricular excitation arose apparently was in the left ventricle, while in case 18 that focus apparently was in the right ventricle.

In figure 4, three electrocardiograms are reproduced that have as a common feature the quality of being essentially normal.

TABLE 1.—*Degree of Cardiac Amyloidosis in 15 Cases*

Type of amyloidosis	Degree of involvement of heart by amyloid		
	Mild	Moderate	Severe
Primary systemic	1	0	3
Complicating multiple myeloma	0	0	1
Localized in the heart	3	3	4

COMMENT

Certain facts that appear pertinent to proper evaluation of these electrocardiograms are included in the legends for these figures. Figure 1 is the only illustration in which all tracings are derived from patients who had severe degrees of cardiac amyloidosis. In case A-4 (fig. 4), the heart was heavily infiltrated by amyloid, yet the electrocardiogram was essentially normal. It is impossible, therefore, to propose any exact correlation between the degree of cardiac involvement by amyloid and the changes encountered in the electrocardiogram. In the absence of such a correlation derived from quantitative considerations, the failure to find a consistently recurring electrocardiographic pattern among all cases

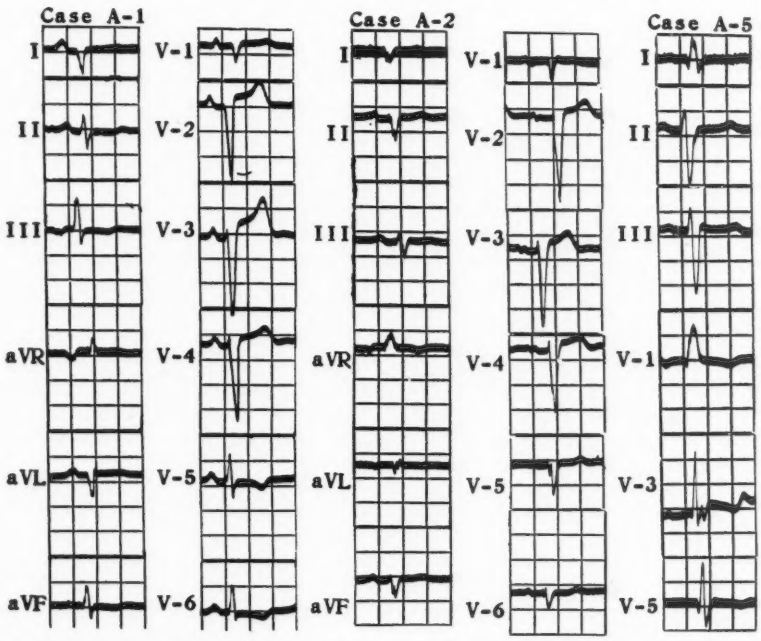

FIG. 1. Primary systemic amyloidosis. *Case A-1:* A 38 year old man whose blood pressure was 122/96. Cardiac amyloidosis was severe. The heart weighed 662 Gm. *Case A-2:* A 54 year old man whose blood pressure was 102/60. He had taken 0.1 mg. of digitoxin daily. Cardiac amyloidosis was severe. The heart weighed 460 Gm. (calculated normal weight = 245 Gm.). *Case A-5:* An 82 year old man whose blood pressure was 150/100. Cardiac amyloidosis was severe. The heart weighed 535 Gm. (calculated normal weight = 353 Gm.).

in the series, irrespective of the degree of cardiac amyloidosis, is not surprising. Certainly the incidence is unusually great of tracings in which the amplitude of the QRS and T deflections in the standard limb leads was low. Auricular fibrillation, present in 7 of the 15 cases, was unusually common, but it must be remembered that in this series only those cases were included in which electrocardiograms had been recorded, and auricular fibrillation is a generally accepted indication for obtaining an electrocardiogram. Prolongation of the P-R interval, a finding in certain cases of cardiac amyloidosis reported in other series,[1, 3] was not encountered in our series, but complete auriculoventricular dissociation was present in two instances.

It is of interest that the tracings were abnormal in 12 of 15 cases of cardiac amyloidosis in which electrocardiograms were recorded, yet in no instance did this abnormality present features typical of or justifiably confused with the findings of acute or old myocardial infarction. In one instance (fig. 2, case 26), the complexes recorded in lead V_5 were consistent with left ventricular hypertrophy, but in the remaining 11 abnormal electrocardiograms, the peculiarities were not those characteristic of

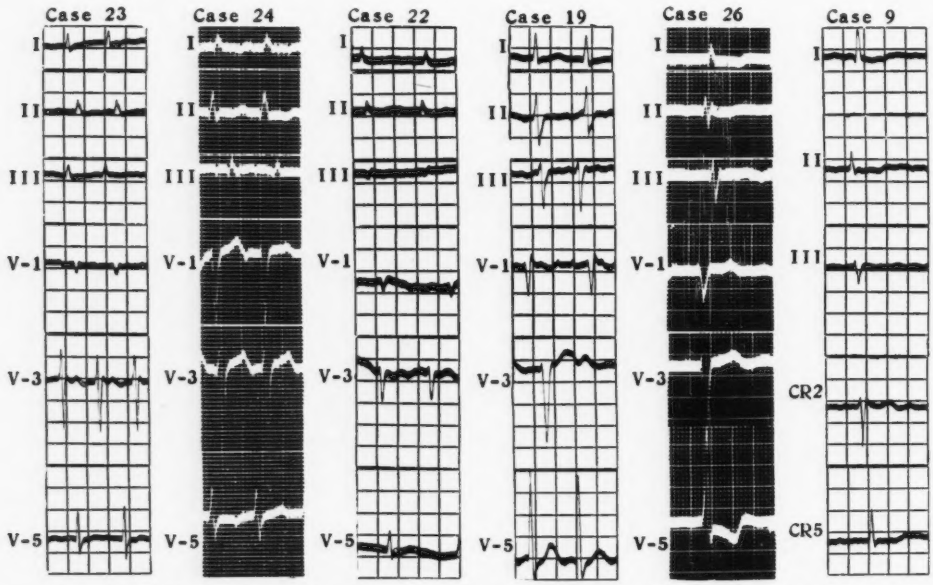

FIG. 2. *Case 23:* An 88 year old woman who died in a state of congestive cardiac failure and whose blood pressure was 100/50. She received digitoxin during the terminal phase of her illness but subsequent to the recording of these electrocardiograms. Cardiac amyloidosis was severe. The heart weighed 455 Gm. (calculated normal weight = 315 Gm.). *Case 24:* A 68 year old man whose death was attributed to bronchopneumonia and whose blood pressure was 135 75. Cardiac amyloidosis was moderate. The heart weighed 440 Gm. (calculated normal weight = 313 Gm.). *Case 22:* A 90 year old man whose death was ascribed to bronchopneumonia and congestive cardiac failure and whose blood pressure was 100/80. He had been receiving digitalis. Cardiac amyloidosis was moderate. Mitral stenosis of mild degree was present. The heart weighed 440 Gm. (calculated normal weight = 370 Gm.). *Case 19:* An 80 year old man who died after a pulmonary embolism and whose blood pressure was 140/90. Cardiac amyloidosis was severe. The heart weighed 450 Gm. (calculated normal weight = 350 Gm.). *Case 26:* A 75 year old man who died in a state of congestive cardiac failure and whose blood pressure was 150/85. He had received digitalis. Cardiac amyloidosis was severe. The heart weighed 875 Gm. (calculated normal weight = 343 Gm.). *Case 9:* A 63 year old woman who died in a state of hepatorenal failure and whose blood pressure was 170/80. Cardiac amyloidosis was mild. The heart weighed 385 Gm. (calculated normal weight = 215 Gm.).

either right or left ventricular hypertrophy. By this devious course, the limited conclusion may be derived that in cardiac amyloidosis the electrocardiogram commonly is abnormal in a manner that fails to identify it with one of the specific patterns of abnormality frequently encountered in patients of advanced age.

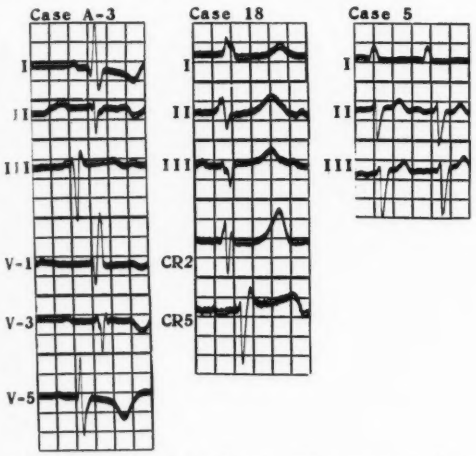

FIG. 3. *Case A-3:* An 81 year old woman on whom a final diagnosis was made of primary systemic amyloidosis with congestive cardiac failure. The blood pressure was 220/80. Treatment with digitalis had been instituted 11 days before the electrocardiograms were recorded. Cardiac amyloidosis was mild. The heart weighed 585 Gm. (calculated normal weight = 215 Gm.). *Case 13:* An 80 year old man on whom a final diagnosis of congestive cardiac failure was made and whose blood pressure was 160/50. Cardiac amyloidosis was severe. The heart weighed 511 Gm. (calculated normal weight = 294 Gm.). *Case 5:* A 78 year old man on whom a final diagnosis was made of carcinoma of the pancreas and whose blood pressure was 130/50. Cardiac amyloidosis was severe. The heart weighed 570 Gm. (calculated normal weight = 343 Gm.).

SUMMARY AND CONCLUSIONS

A study has been made of the electrocardiograms obtained from 15 patients who had cardiac amyloidosis of various types. If the clinician is to recognize the existence of cardiac amyloidosis, he is most likely to arrive at the diagnosis by defining the presence of amyloid elsewhere in the body, as in primary systemic amyloidosis, or by identifying a disease, namely, multiple myeloma, that predisposes to amyloidosis.

If the deposits of amyloid are limited to the heart, then a method for positive diagnosis by clinical means is not evident. Suspicion that such a process exists may be entertained when congestive cardiac failure is encountered in an elderly individual unafflicted with the usual causes of such failure.

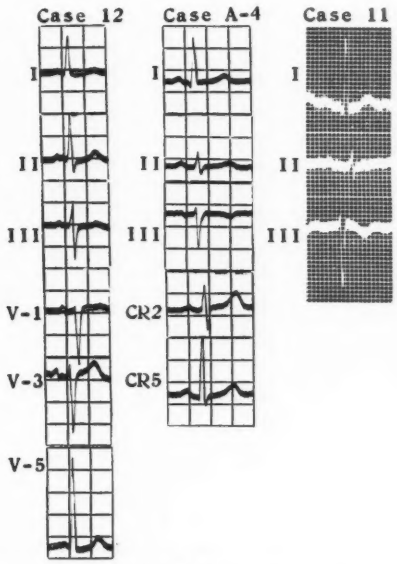

FIG. 4. *Case 12:* An 84 year old woman on whom final diagnosis included perforated peptic ulcer, peritonitis and congestive cardiac failure. The blood pressure was 158/60. Cardiac amyloidosis was mild. The heart weighed 250 Gm. (calculated normal weight = 215 Gm.). *Case A-4:* A 65 year old woman on whom a final diagnosis was made of amyloidosis complicating multiple myeloma and whose blood pressure was 146/92. Cardiac amyloidosis was severe. The heart weighed 440 Gm. (calculated normal weight = 244 Gm.). *Case 11:* A 75 year old man on whom a final diagnosis was made of carcinoma of the bladder and whose blood pressure was 160/100. Cardiac amyloidosis was moderate. The heart weighed 405 Gm. (calculated normal weight = 333 Gm.).

Definitive evidence cannot be had from the electrocardiogram, but suspicion may be aroused by a tracing in which the standard limb leads disclose QRS complexes and T waves of low amplitude, by a tracing affording evidence that auriculoventricular conduction is impaired or blocked or by a tracing disclosing auricular fibrillation. Finally, these

tracings usually possess peculiarities that conform to none of the specific patterns of abnormality commonly encountered in patients of advanced age.

Sumario Español

Los hallazgos electrocardiográficos fueron analizados en 15 pacientes que durante la autopsia se le encontraron depósitos de amiloide en el corazón. Aunque 12 de los 15 trazados se consideraron anormales, cambios que se pudieran considerar específicos de amiloidosis cardíaca no se han podido definir. Las alteraciones más comunes encontradas fueron, fibrilación aurícular, complejos QRS y ondas T de poca amplitud en las derivaciones regulares de las extremidades y deterioro en la conducción aurículoventricular.

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Isolated U Wave Negativity

By J. H. PALMER, M.D.

Inversion of U as the only abnormal electrocardiographic finding is here shown to be the first change to occur in certain cases of hypertension, coronary artery sclerosis, and other organic heart disease. It is also found in association with certain metabolic and electrolyte changes. Its recognition will enhance the value of the electrocardiogram in clinical diagnosis.

THE CLINICAL significance of inverted U waves has received scant attention from cardiologists. Although its association with other electrocardiographic abnormalities has been described,[1-3] this has not contributed significantly to diagnosis or prognosis.

Reports of only a very few cases of isolated U wave negativity have appeared in the literature. Nahum and Hoff[1] reported two, Papp[2] one, and Palmer[4] four. In every case the finding was considered abnormal. On the other hand, Katz[5] has observed that "little clinical weight would be given to an electrocardiogram in which the only deviation from the normal was in the U wave." The author has shown[4] that U may temporarily become negative during exercise tests for angina pectoris, suggesting that such inversion should be regarded as one of the criteria of acute coronary insufficiency. Valuable confirmation of this is afforded by the later, but apparently independent, observations of Holzmann.[6]

The physiology of the U wave is imperfectly understood. Hoff and Nahum[7] concluded that it forms part of the ventricular complex and is coincident in time with the supernormal phase. Zuckermann and Cabrera[8] have suggested that it originates in the interventricular septum and is a result of retardation of repolarization in that structure by the compression brought to bear on it by both ventricles. Zuckermann and Estandia[9] later claimed support for this hypothesis by showing that while extrasystoles originating in the ventricular walls usually appear coincidentally with the U wave, those originating in the septum appear after the U wave, that is, at the end of the septal refractory period.

It was felt that while an analysis of clinical records might add little to our knowledge of the causation of the U wave, much might be learned concerning its incidence and clinical significance. Such empirical knowledge is long overdue.

METHOD

The present communication is based on the findings in approximately 10,000 electrocardiograms personally read by the author in the course of a four-year period during which each tracing was especially observed for negative U waves. Many of the tracings had actually been taken previously and came to notice when being compared with more recent ones. About 7,000 are from a Veterans' hospital where the population is all adult and preponderantly male, 500 are from a children's hospital, and the remainder from a general hospital and from private practice. About two-fifths of the tracings read were normal.

Electrocardiograms were admitted to the series if, apart from U wave negativity, all the leads taken on any one occasion could be regarded as probably within normal range for the patient's age.

U wave negativity that was just perceptible has been accepted, providing it was constant. Alternating current interference will frequently make it difficult or impossible to determine these minor grades; a higher incidence will therefore be found if electrocardiographs are used which minimize or eliminate this interference. We have not resorted to increasing the camera speed, as practiced by Groedel and Miller[10]; they claim by this method a better detection of U waves.

It is frequently found, especially in the right chest leads, and even as far to the left as C_4, that a normally upright T is followed by a negative depression which occupies the period between T

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Read on June 9, 1952 before the Canadian Heart Association, Lake Louise, Alberta, Canada.

and a positive U. The author has evidence (unpublished data) which suggests that this T-U period is intimately related to the succeeding U wave and may form part of a U complex actually beginning at the end of T. This impression is supported by the observation that diphasic U waves occur and are usually −+ in character. They may be seen usually

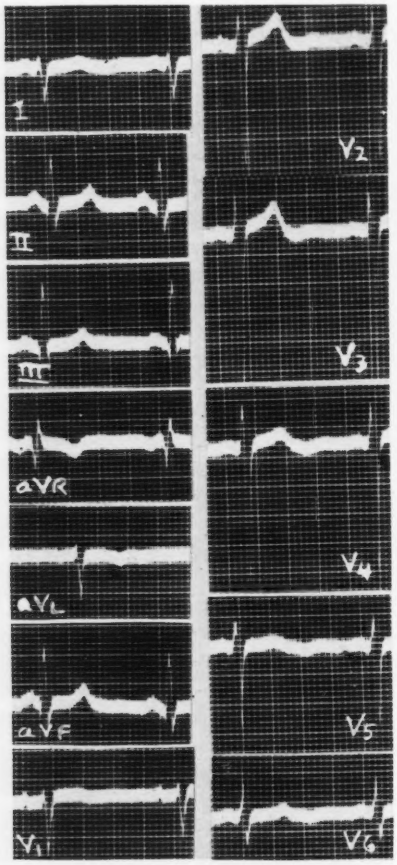

FIG. 1. (Case 31.) Hypertension. Tall thin male with vertical heart showing high degree of clockwise rotation. Negative U waves can be recognized in leads I, aV_L, V_4, V_5, V_6, and a positive U wave in aV_R.

at about the C_3 position; as the exploring electrode moves further to the left the apex of the U wave negativity concurrently moves further away from QRS (fig. 1).* The matter is still sub judice; in the meantime and for purposes of this paper such T-U depression and diphasic U waves have not been considered as negative U waves. (See fig. 2.) Identification of a negative U is best made by determining the end of T in other leads and transferring this measurement to the lead in question. In most of the cases in the present series a short isoelectric period between the end of T and the beginning of the negative U could be recognized. Acceleration of the heart rate may cause considerable shortening of the Q-U duration.[4]

It early became apparent that negative U waves in lead aV_R were almost as frequently found in clinically normal patients as were upright U waves in other leads. They were assumed to be normal, analogous to the negative T waves seen normally in this lead, and were consequently disregarded. Conversely a positive U in aV_R would be considered abnormal; an example of this is shown in figure 1.

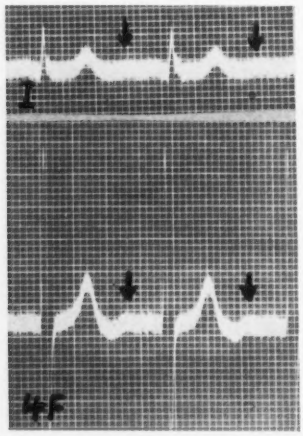

FIG. 2. To illustrate depression of T-U junction which may cause confusion with negative U wave. Arrows mark positive U waves.

INCIDENCE

U wave negativity, either isolated or associated with other electrocardiographic abnormalities, was recognized in 165 patients. Ten patients seen early in the investigation (four with isolated U wave negativity) have already been described elsewhere.[4] They are included above for statistical purposes, but do not form part of the group to be analyzed below.

In the 500 children's records there was found only one tracing showing negative U waves. This lowered incidence, compared with that in adults, is striking, especially as positive U waves are common in normal children. The

* A good example of this was discovered in a tracing published by Dressler, Roesler, and Lackner[11] to illustrate notching of T waves (their fig. 4).

most satisfactory explanation appears to be that the rapid heart rate found normally in infants, usually in sick children, and frequently in healthy children, results in such an approximation of T and P waves that U cannot be recognized satisfactorily.

Fifty-two *patients* with isolated U wave negativity were found, one for each 200 tracings examined. Some of these patients had two or more examinations, so that the actual percentage of abnormal *tracings* is considerably higher.

It is a defect in the investigation that unipolar limb leads and multiple chest leads were not taken in every case; had this been done it is possible that some added electrocardiographic abnormalities would have been found, especially in chest leads further to the left in patients with hypertension. Of the 18 patients in the group who had had less than three chest leads in addition to leads I, II, and III, 15 actually had hypertension; all of these had normal-sized hearts (12 proven by x-ray examination), and in three patients subsequent multiple lead tracings proved normal. It is not felt, therefore, that the incidence described above would have been significantly different had 12-lead tracings been made in every case, and moreover such extra leads could well have increased the number of negative U waves found.

In table 1 is recorded the frequency with which negativity occurred in each lead. By far the highest incidence was in chest leads made at the fourth, fifth and sixth precordial positions, in that order. This was reflected to a lesser degree in lead I where negativity did not occur unless at the same time the left chest leads or lead aV_L was also involved. No changes were found in C_1 and C_2. The writer has seen only one case of U wave negativity in the right chest leads,[4] and its rarity in this region has been confirmed by Groedel and Miller.[10] In only two cases was U negative in lead III, and lead aV_F was normal throughout.

Analysis of Cases

Table 2 presents in summary form the diagnoses and pertinent details of the collected cases.* Roentgenograms of the chest were available in all but four. In 40 the heart was normal in size, in two it was enlarged, and in two others probably enlarged. In the four without x-ray examination (these are indicated in the table) the heart was normal by clinical tests. The blood pressure readings mentioned were, with one exception, made at approximately the same time as the electrocardiograms. Omission of blood pressure records from the table indicates that the patient was normotensive.

By far the commonest pathologic condition associated with isolated U wave negativity was found to be hypertension. If the two cases of chronic glomerulonephritis with uremia, in which hypertension was serious, are included, it accounted for 26, more than half

Table 1.—*Incidence of Isolated U Wave Negativity in Various Leads (48 Cases)*

I	II	III	aV_R	aV_L	aV_F
11 (48)	3 (48)	2 (48)	—	3 (9)	0 (9)
C 1	C 2	C 3	C 4	C 5	C 6
0 (12)	0 (28)	1 (7)	44 (46)	17 (20)	5 (15)

Figures in parentheses indicate number of times lead recorded. C indicates chest lead V or F.

of the total number. In four more it was associated with angina pectoris.

In one patient of the hypertension group (case 31) the tracing was made while the patient was in hospital for cystoscopic investigation of his chronic pyelonephritis and albuminuria. At that time a single normal blood pressure reading was recorded. Six months later the blood pressure was 190/120, and it has since then remained at about this level. The patient was probably hypertensive at the time of the first examination, and has been so classified.

The next largest group is that resulting from coronary sclerosis. It includes nine patients with angina pectoris (four with hypertension, mentioned above), one with coronary occlusion seen in the early stage, and three (cases 7, 21, 34) who, it was assumed on clinical grounds, had asymptomatic coronary sclerosis. In sup-

* At the request of the Editor table 2 is being omitted. It will be furnished upon request.

port of this diagnosis it is pointed out that one of the three had experienced earlier a paroxysm of auricular fibrillation, another became hemiplegic soon after observation and later developed auricular fibrillation, while the third had an aortic systolic murmur probably indicative of calcific aortic stenosis; all of them were past the age of 75 and were considered senile. The high incidence of extensive coronary sclerosis at necropsy in this age group is well known. Storch and co-workers[12] have found electrocardiographic changes characteristic of coronary insufficiency in some aged asymptomatic individuals subjected to Master's standardized exercise tolerance test.

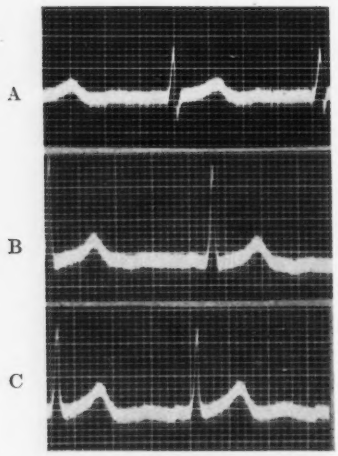

FIG. 3. (Case 6.) Hypertension. Lead IVF: (A) Sept. 1942, (B) Feb. 1950, (C) May 1951. Note negative U in tracing (B) only. Blood pressure was of same general level on each occasion.

Subsequent reversion of negative U waves to positive (fig. 3) was seen in seven cases of the series, and six of these were in the hypertension and coronary sclerosis groups. In one patient with hypertension (case 27) the tracing was found to be normal as long as five years, and in one with angina pectoris (case 1) three years, after the U wave inversion had been first seen.

The group with valvular disease comprised three cases. One patient had aortic regurgitation with a history of both rheumatic fever and syphilis, another (the only child in the series) had chronic rheumatic mitral disease, and the third had the classic signs of calcific aortic stenosis. The common etiologic agent, if one were sought, would probably be early left ventricular hypertrophy.

An interesting group was found in which the only obvious common factor was elevation of the serum phosphatase level. Two were cases of carcinoma of the prostate (cases 15 and 23, fig. 4), one with bone metastases; in neither of them could any obvious cardiovascular disease be made out. Two patients (cases 19 and 44) had Paget's disease with high alkaline phosphatase levels; in one of them there was associated hypertension, which of course might itself have affected the U wave. In three of the four cases the serum phosphorus level had been recorded as normal, and in the

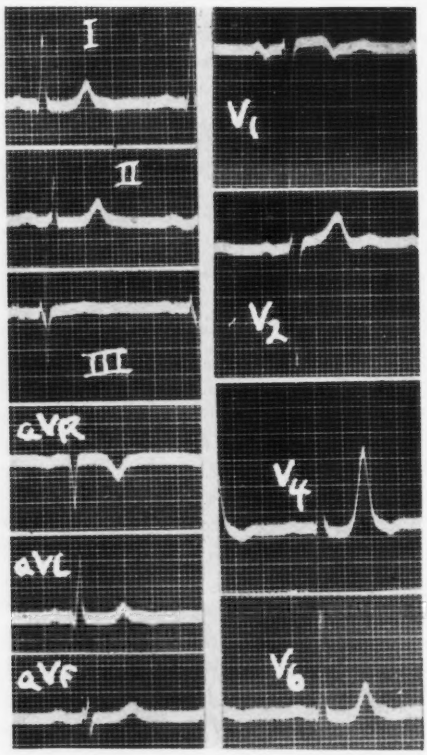

FIG. 4. (Case 23.) Carcinoma of prostate. Note negative U in leads I, aV_L, V_4, V_6, and slightly positive U in aV_R. The T wave in V_4 is high and probably abnormal.

only one in which the serum potassium level had been estimated it also was normal. Serum calcium determinations were not made, but it is unusual for them to be abnormal in either of these two diseases. Whether the high phosphatase level is the actual cause of the U wave inversion is a problem which requires further investigation. In Paget's disease another possibility is the load imposed on the heart by the oftentimes greatly increased cardiac output. Such an argument however cannot apply where prostatic cancer is concerned.

The electrocardiographic changes characteristic of hypokalemia are now well known. One of these signs is a prominent positive U wave in the right chest leads. In a patient (case 17, fig. 5) with potassium loss due to carcinoma of the pancreas with small bowel obstruction, a positive U wave of 1 mm., which is large but well within the arbitrary normal limit described by Katz,[5] was seen in V_2; there were no RS-T or T wave changes, and the Q-T interval was just within the normal limits. U was negative in leads I and V_6. At necropsy the myocardium and coronary vessels were found to be healthy. One seems justified in regarding the U wave changes, both the increased positivity on the right side of the chest and the negativity on the left (they are probably reciprocal), as results of the electrolyte disturbance. Nadler and co-workers[13] found that the U wave present in CR_4 during hypokalemia in diabetic acidosis could be abolished by potassium salts given intravenously, and concluded that U is in some way related to disturbance in electrolyte balance. In any event it would seem that the U wave change is an early one, and that the development of a so-called hypokalemic myocarditis[14] is not essential for its production.

One case of myxedema (case 37) is included. Here the electrocardiogram showed low voltage, but normally directed, T waves; because of its borderline abnormality, it was admitted to the series. Its interest lies in the fact that disappearance of the U wave negativity, present in leads I and V_4, was the first change to occur after thyroid treatment was begun. Only later did QRS and T wave voltages increase.

In one case no satisfactory explanation for the U wave negativity could be found. The patient (case 36) had been admitted to hospital for cholecystectomy. No abnormal cardiovascular symptoms or signs were discovered; the blood pressure was normal. Unfortunately it was not possible to trace her subsequently.

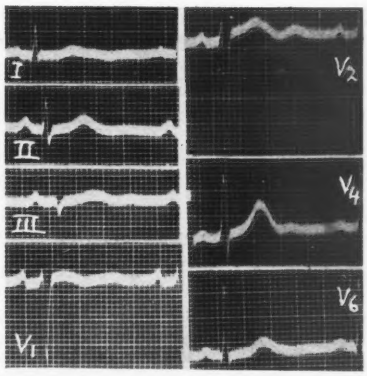

FIG. 5. (Case 17.) Small bowel obstruction with hypokalemia. U wave negative in leads I and V_6. U is unusually high in V_2.

SUMMARY AND CONCLUSIONS

It has not been the purpose of this communication to determine the mechanism by which U wave negativity is produced, but rather to estimate its frequency and its significance.

Isolated U wave negativity is found in about 1 per cent of routine electrocardiograms from general hospital practice. It is rare in infants and children. Its association with certain diseases, most of which have well-recognized cardiac manifestations, leads to the conclusion on empirical grounds that it is probably always pathologic.

U wave inversion without other electrocardiographic change is seen in patients with hypertension more often than in all other conditions combined. Coronary sclerosis yields the second highest incidence. In both of these diseases and in certain valvular lesions the abnormality is probably related to organic changes in the myocardium. In other conditions in which it was found in the present series, notably Paget's disease, carcinoma of the prostate, hypokalemia, and myxedema, the abnormal process may be biochemical.

The change is an early one, preceding the classic electrocardiographic findings of such chronic diseases as hypertension and coronary sclerosis sometimes by years, and is also reversible.

Recognition of isolated U wave negativity as an early pathologic finding will increase the diagnostic value of the electrocardiogram. Discovery of its association with other diseases than those included in the present series is predicted.

Addendum

Since the above article was prepared for publication 11 further patients have been seen who showed isolated U wave negativity. The diagnoses were as follows: hypertension, six; angina pectoris, one; syphilitic aortic regurgitation, one; calcific aortic stenosis, one; gout, one; pulmonary tuberculosis with duodenal ulcer but without obvious cardiovascular disease, one.

Sumario Español

Inversión de la U como el único hallazgo anormal electrocardiográfico es demostrado ser el primer cambio en ocurrir en ciertos casos de hipertensión, esclerosis coronaria y otras enfermedades del corazón orgánicas. También se observa este cambio en asociación con ciertos cambios metabólicos y electrolíticos. Su reconocimiento aumentará la importancia del electrocardiograma en el diagnóstico clínico.

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Coccidioidal Pericarditis

By ROGER LARSON, M.D., AND ROBERT E. SCHERB, M.D.

In endemic areas where coccidioidomycosis is encountered, pericarditis of an occult etiology warrants a careful search for coccidioidomycosis. A coccidioidin skin test is helpful. The established diagnosis, however, depends upon positive coccidioidal complement fixation and precipitin tests, or recovery of the organism from the sputum or the pericardial fluid.

COCCIDIOIDOMYCOSIS is a disease that occurs endemically in the San Joaquin Valley, although it is found also in arid regions of Arizona, New Mexico and Western Texas. The causative organism is a fungus, *Coccidioides immitis* (Rixford and Gilchrist, 1896).[1] Before World War II it was generally conceded that a physician residing outside such endemic areas needed only a "reading acquaintance" with this disease. At the present time this concession is no longer tenable, since 6,000 to 8,000 new cases have been shown to have existed in clinically recognizable forms in transient military personnel from various military installations in these endemic areas. An increased number of cases have also been found throughout other supposedly coccidioidal-free areas, the only past history of exposure being that the subject has passed through endemic areas either by bus, automobile or train.

Excellent reviews have been presented by Forbus from material collected from the Armed Forces Institute of Pathology[3] and by Schwarz and Muth,[6] each with their attendant bibliographies. It is sufficient to note that the reported cases of cardiac and/or pericardial involvement were limited to those of disseminated coccidioidal involvement.[2, 3]

Briefly, to aid in following the data presented, it is of interest to note that disseminated coccidioides is much more prevalent in Negroes and Filipinos than in members of the white race.[6]

Erythema nodosum occurs approximately about 8 to 15 days after onset of the disease in 5 per cent of all cases and in 20 per cent of all symptomatic cases.

Skin testing by coccidioidin (made from cultures of *Coccidioides immitis*) shows that 60 per cent of the positive skin reactors have had no history of clinical symptoms due to the disease. Skin testing will not cause future sensitization to skin testing nor produce positive precipitin or complement fixation reactions. However, it will often precipitate or exacerbate erythema nodosum or multiforme. Skin sensitivity lasts from 1 to 10 years, the latter being the most usual. The most important skin sensitivity reaction is the "change-over" reaction, symbolizing recent infection. The appearance of such sensitivity may occur 10 to 45 days after exposure or 2 to 21 days after onset of the disease.

The disseminated type is four times more frequent in Negroes and 18 times more frequent in Filipinos than in the white subjects, the incidence being approximately 1:500 in the white race. In acute disseminated coccidioides 70 per cent will fail to react to any dilution, whether it is 1:100, 1:10 or undiluted coccidioidin. Cross reaction may be found to histoplasmosis or blastomycosis.

Diagnosis by culture and direct smears is not so efficacious as by tissue biopsy.

Complement fixation and precipitin tests are the most reliable tests for diagnosis and prognosis. The precipitin test becomes positive in low-grade primary infection, and persisting through, becomes negative before the complement fixation test; the latter remains positive much longer. The complement fixation test may never become positive with mild infection of primary type but is prognostic when positive in the disseminated form. Oddly enough, it is oftentimes negative with cavitation.

From the Internal Medicine Department, Kern General Hospital, Bakersfield, Calif.

Thus we may present the following chart:

	Skin Test	*Precipitin Test*	*Complement Fixation*
Acute benign infection	+	− or +	−
Acute severe, focal, not disseminated	+	+	− or +
Disseminated	− (70%)	+ or −	+

The sedimentation rate has been found elevated by all observers. In patients with cavitation, the sedimentation rate is normal in at least 70 per cent. A fall in the sedimentation rate is a good prognostic sign.

X-ray review shows that the areas of parenchymatous lung involvement are most often in the midlung region, followed by lower lobe involvement, the least affected being the apical region.

TABLE 1.—*Serologic Studies in Case 1*

Date	Precipitin Test	Complement Fixation						
		Sed. Rate	½	¼	⅛	1/16	1/32	1/64
2/21/51	0	26	0	0	0	0	0	0
3/12/51	0	28	0	0	0	0	0	0
3/21/51	0	28	4+	4+	4+	3+	0	0
4/3/51	0	36	0				0	0
4/20/51	0	29	4+	4+	0	0	0	0
7/24/51	0	3	0	0	0	0	0	0

The literature is replete on the pathologic findings on the various forms of coccidioides. Microscopically, it is known that a specific tissue reaction accompanies the different developmental stages of the spherule and that the coccidioidal granuloma is rather pleomorphic, though sufficiently characteristic to lead to a suspicion of a specific granulomata and to a search for the offending pathognomonic spherules.

Detailed reports of three cases of coccidioidal pericarditis with the autopsy finding on one are presented. These are unique in that they showed no evidence of dissemination beyond the pericarditis. Two cases were diagnosed clinically and have been followed for about one year without any signs of progression of the disease. One was discovered at autopsy as an incidental finding.

CASE REPORTS

Case 1. C. W., a 49 year old Negro man, was admitted to the hospital on Feb. 20, 1951, with the chief complaint of chest pain. This involved the lower end of the sternum with radiation to the left shoulder and felt like a "great pressure" in the sternal region. The patient had experienced some dyspnea and cough since the onset of his present illness. The past and family history were of no additional value.

Physical examination revealed a well-developed well-nourished Negro man who was in severe pain. The temperature was 37.5 C., pulse 84, respirations 18, and blood pressure 110/70. Examination of the lung fields revealed no abnormal findings.

A loud, harsh precordial friction rub was heard in the third and fourth intercostal spaces, just to the left of the sternum. The heart tones were somewhat faint. No murmurs were heard. The cardiac rhythm was regular.

The following day the friction rub had completely disappeared. The patient ran a febrile course from 37.5 to 38 C. for the first week of hospitalization and remained afebrile thereafter. For two weeks he continued to have exacerbations and remissions of his substernal pain. The total period of hospitalization was six weeks. He was last seen in the outpatient clinic on Dec. 21, 1951, at which time he was asymptomatic and doing hard agricultural labor. Physical examination at that time was entirely normal.

Laboratory Data: The while blood cell count was 6,700, with 78 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes and 5 per cent monocytes. The sedimentation rate was 26 mm. in one hour. The Kahn test was negative. A chart of the serologic reactions is presented in table 1. The skin test with coccidioidin was positive and the Mantoux test was negative at 1:100.

An x-ray film made on Feb. 26, 1951 (fig. 1) showed an infiltrative process in the lower portion of the right lung field compatible with an acute pneumonitis. On March 20 (fig. 2) there was almost complete clearing of the infiltration.

The features of the electrocardiogram made on Feb. 21, 1951 are shown in fig. 3. The total picture was that of a diffuse subepicardial injury, which is characteristic of pericarditis. The electrocardiogram had returned to normal by December 21.

In summary, this 49 year old Negro man was admitted to the hospital because of severe substernal pain. The findings of a pericardial friction rub on physical examination and the characteristic changes in the electrocardiogram established the diagnosis of pericarditis. The etiology was established by the findings of pneumonitis on x-ray study, a positive coccid-

oidin skin test and a positive complement ixation test for coccidioidomycosis. The even- ual course over a nine-month period of follow- ıp was one of complete recovery without dis- emination.

Case 2. W. T., a 26 year old Negro man, was dmitted to the hospital on Aug. 20, 1950 because f fever and substernal pain for two days. The pain as dull and constant in character and was aggra- ated by respiration. The patient also complained f fever, chills, headache and nausea.

Physical examination revealed a well developed, ell nourished Negro man who was acutely ill. The lood pressure was 120/70, pulse 130, respirations 0, and temperature 40.6 C.

On examination of the lungs a few scattered post- ussive rales were heard posteriorly in both lower ung fields. There was no impairment of resonance nd the breath sounds were normal. The cardiac ate was 130 and the rhythm was regular. No mur- murs or friction rubs were heard.

The patient remained febrile for 11 days with a gradual subsidence of the temperature to normal. He continued to complain of some precordial and substernal pain until a few days before discharge on Sept. 19, 1950.

Laboratory data: The hemoglobin was 11.3 Gm. The white blood cell count was 9,200 with 76 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes. The sedimentation rate was 30 mm. in one hour. The coccidioidin skin test was positive and the Mantoux test negative. Coccidioidal serologic reactions are summarized in table 2. Three concentrated sputum specimens were negative for tubercle bacilli on smear and one on culture.

X-ray films of the chest made on Aug. 24, 1950 showed a definite infiltrative process extending from the left hilar area to the left first anterior intercostal space with prominence of the left hilar area, suggestive of hilar adenopathy.

An electrocardiogram made on Aug. 31, 1950 (fig. 4) showed findings compatible with the diagnosis of pericarditis.

Second admission: The patient was readmitted on Oct. 12, 1950 for left precordial pain. Because of the severity of the pain the admission diagnosis was said to be possible myocardial infarction. At this time physical examination was entirely negative, except for a temperature of 37.5 C.

The coccidioidal serologic findings are shown in table 2. Seven concentrated sputum specimens were negative for tubercle bacilli on smear and three ultures were negative for *Mycobacterium tuberculo- is* and *Coccidioides immitis.*

Subsequent admissions: The patient was admitted n three more occasions with the same complaint of precordial or substernal pain. On each occasion the occidioidal serology was elevated and the electrocardiogram showed similar abnormalities. A summary of some of the laboratory work is presented in table 2.

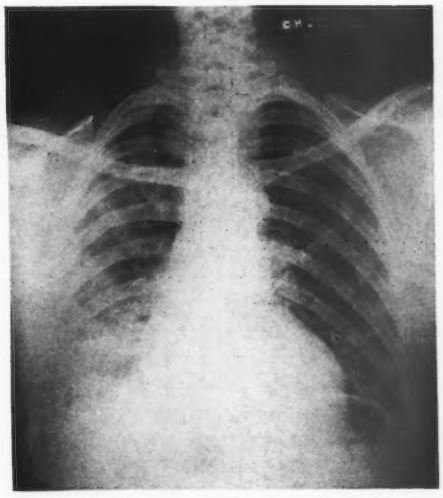

FIG. 1. C. W. Case 1. Posterior-anterior teleroentgenogram of the lungs taken Feb. 26, 1951 showing infiltration in right lung compatible with coccidioidomycosis.

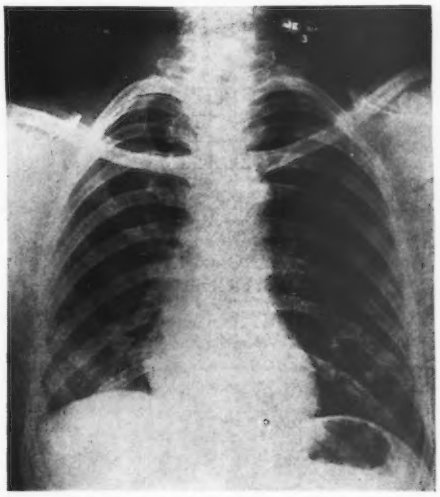

FIG. 2. C. W. Case 1. Posterior-anterior teleroentgenogram of the lungs taken March 20, 1951 showing partial clearing of infiltration in right lung. Infiltration compatible with coccidioidomycosis.

In summary, this 26 year old Negro man was admitted to the hospital on several occasions for substernal or precordial pain. No

friction rub was ever heard, but the electrocardiograms presented sufficient abnormality ity, complement fixation and precipitin tests. The patient was lost to follow-up after a year.

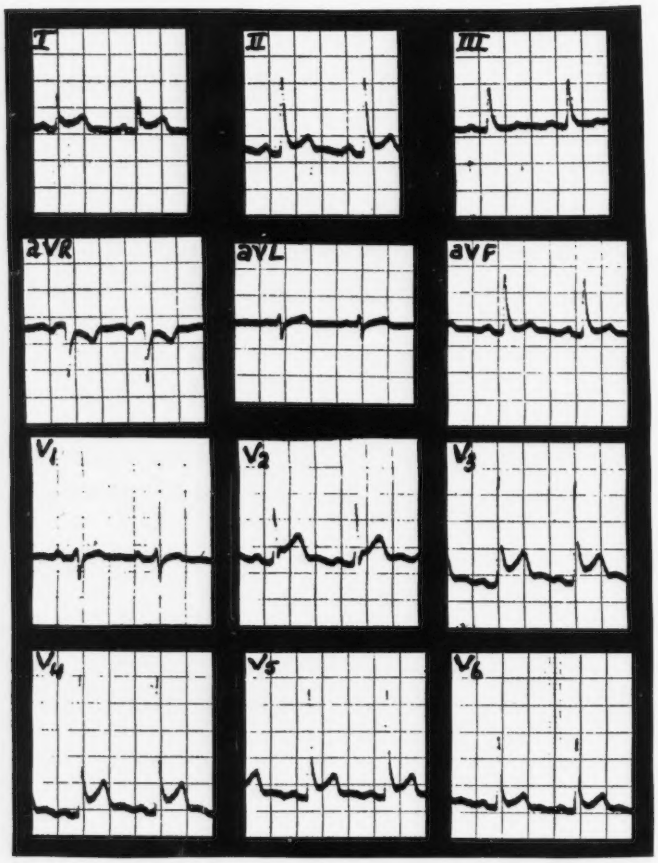

FIG. 3. C. W. Case 1. Electrocardiogram taken Feb. 21, 1951. Findings of elevation of S-T segment noted in all limb leads and in V leads. Elevation most marked in the V leads and compatible with pericarditis.

TABLE 2.—*Serologic Studies in Case 2*

Date	Precipitin Test							Complement Fixation									
	Sed. Rate	Undil.	1/10	1/40	1/100	1/200	1/400	1/2	1/4	1/8	1/16	1/32	1/64	WBC	N	L	E	M
8/21/50	30	4+	4+	4+	0	0	0	1+	0	0	0	0	0	9200	76	24	0	0
10/4/50	32	4+	4+	4+	0	0	0	4+	4+	3+	1+	0	0	5600	41	49	8	2
10/30/50		4+	4+	4+	0	0	0	4+	3+	2+	0	0	0					
2/7/51	23	0	0	0	0	0	0	4+	4+	4+	3+	0	0	7100	51	43	8	1
7/24/51		0	0	0	0	0	0	4+	4+	2+	0	0	0	4950	37	51	5	7

in the S-T and T segments to be compatible with a diagnosis of pericarditis. The coccidioidal etiology was established by skin sensitiv- At that time he had showed no evidence of dissemination, but his serology remained elevated.

Case 3. W. W., a 60 year old white man, first ·ame to the outpatient clinic of Kern General Hos-)ital on Dec. 20, 1949 with the complaint of cough ınd weight loss. An x-ray film of the chest revealed ı lesion in the left apex. Skin test for tuberculosis (Mantoux) was negative but the coccidioidin skin test was positive. Two concentrated sputum speci-mens were negative for acid-fast bacilli, and one

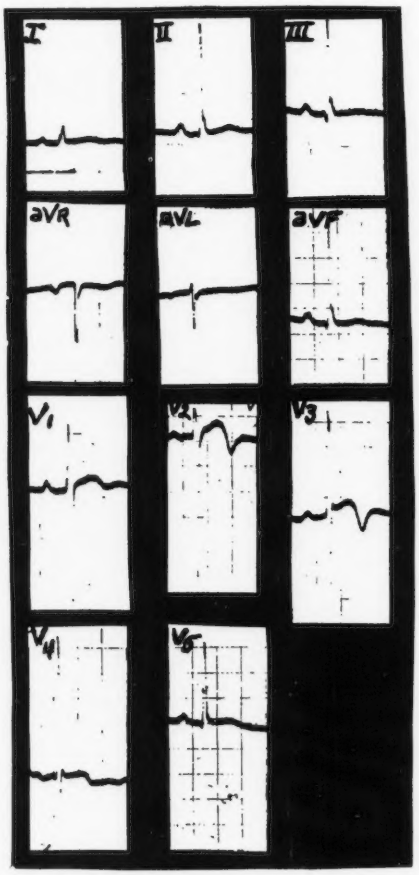

FIG. 4. W. T. Case 2. Electrocardiogram taken on Aug. 31, 1950. Elevation of S-T segment in all limb leads and V leads. Elevation most pronounced in V_1 and V_4. Negative waves forming in leads V_1 to V_4. No Q waves seen. Diagnosis: pericarditis.

gastric washing was negative on direct smear and guinea pig inoculation. The patient refused hospitalization for further study and was not seen again until Jan. 22, 1951 at which time he was in a state of congestive failure.

Physical examination revealed a well developed, poorly nourished white male who was slightly dyspneic at bed rest. The chest was typically emphysematous. No rales were heard. The heart tones were somewhat soft and the second aortic and pulmonic sounds were equal. Blood pressure was 110/70. The abdomen was scaphoid in contour. Liver dullness could be percussed 5 cm. below the costal margin at the right midclavicular line. There was a plus 2 pitting edema of the ankles.

The patient did not respond to treatment with salt-free diet, digitalis and mercurial diuretics. He became progressively worse and he expired on Feb. 2, 1951 approximately 11 days after admission.

Laboratory data: The hemoglobin was 9.9 Gm. The red blood cells numbered 3,620,000 and white blood cells 20,050. A differential count revealed 76 per cent polymorphonuclear leukocytes with 7 per

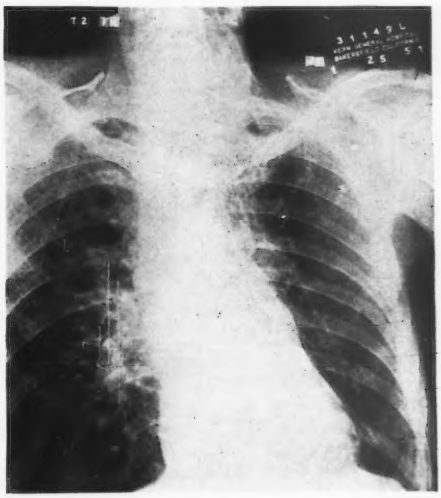

FIG. 5. W. W. Case 3. Posterior-anterior teleroentgenogram of lungs Jan. 25, 1951. Markings of right lung that were first interpreted as possible tuberculosis later found to have been coccidioidomycosis, healed. Bullous emphysema at bases.

cent stab forms, 20 per cent lymphocytes and 7 per cent eosinophiles. The nonprotein nitrogen was 56 and creatine 1.5 mg. per 100 cc. The Kahn test was negative. The coccidioidin skin test was positive and the Mantoux negative.

X-ray films of the chest read on Jan. 25, 1951 (fig. 5) showed a marked pulmonary emphysema. In the central and upper lung fields the markings were dense and increased, suggesting old fibrosis.

The electrocardiographic pattern is shown in figure 6 (patient on digitalis).

Autopsy: Only the gross and microscopic findings of the heart and lungs are given with a list of final anatomic diagnoses.

The heart weighed 640 Gm. The parietal pericardium was densely adherent to the epicardium

over the entire heart. In a few areas over the anterior portion of the heart the pericardium could be separated with difficulty from the epicardium. The myocardium was reddish brown and showed no evidence of scarring or fibrosis.

The lungs were large, voluminous and very crepitant to palpation. There were numerous emphysematous bullae on the surface of the lung, especially marked at the left base. In the region of the left apex the lung showed dense adhesions. On cutting through this area a section was discovered with

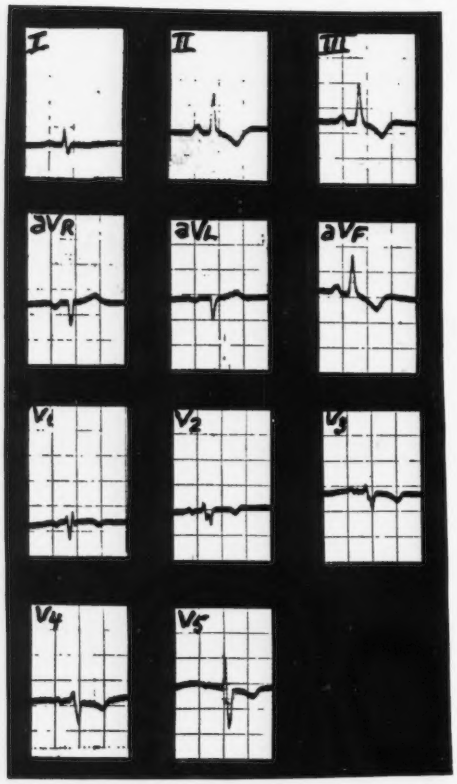

FIG. 6. W. W. Case 3. Electrocardiogram taken July 22, 1951. Vertical heart position with marked clockwise rotation. Digitalis effect noted.

little lung tissue but made up primarily of granulomatous or fibrous tissue and containing numerous smooth-lined spaces, presumably dilated bronchioles. This was thought to be an area of bronchiectasis.

Microscopically the myocardial fibres were well preserved. Several distinct small granulomas were seen in the thickened pericardium. These consisted of centers of necrosis, surrounded by epithelioid cells. Several giant cells of the Langhans type were seen in the granuloma. One of these giant cells contained a clear spherical body with a definite wall or capsule. This was interpreted as a spherule of *Coccidioides immitis*. Acid-fast stains of the pericardium failed to reveal any acid-fast bacilli. A slide stained by the Hotchkiss-McManus[4] technic for fungi revealed one spherical body, which took a light red stain.

Sections through the lesion in the left apex revealed many granulomas, consisting of necrotic centers surrounded by epithelioid cells and lymphocytes. Giant cells of the Langhans type were again seen in these granulomas. Acid-fast stains failed to reveal any acid-fast bacilli. Slides stained by the Hotchkiss-McManus technic for fungi revealed several spherules of *Coccidioides immitis*.

In summary, this 60 year old white man was admitted to the hospital in congestive heart failure and expired 11 days later. X-ray films of the chest showed fibrosis in the upper lung fields and marked pulmonary emphysema. The coccidioidin skin test was positive and the Mantoux test negative. Previous sputum specimens had been negative for tubercle bacilli on smear, culture and guinea pig inoculation. The clinical diagnoses were pulmonary fibrosis and emphysema with cor pulmonale. These diagnoses were substantiated at autopsy, but in addition a totally unsuspected chronic adhesive pericarditis was discovered. A clue to the etiology was found in some granulomatous lesions in the apex of the left lung which microscopically revealed small granulomas containing spherules of *Coccidioides immitis*. Granulomas of the same microscopic structure were found in the pericardium. Special stains of the pericardium and lung failed to reveal any acid-fast bacilli. One probable spherule was seen in a giant cell in the pericardium.

In view of both the positive and negative findings it was felt justified to make the diagnosis of chronic adhesive pericarditis, due to coccidioidomycosis.

DISCUSSION AND SUMMARY

Pericarditis is a well-known complication of pulmonary tuberculosis. This is generally considered to be the result of retrograde lymphatic extension or contiguous spread from a pulmonary source.[7] It would be strange, therefore, if coccidioidomycosis, which so characteristically involves the hilar lymph nodes, did not occasionally produce pericarditis without generalized dissemination. Yet a search of the

medical literature failed to reveal any completely documented case reports of this complication. Three cases which the authors feel justify the recognition of such an entity have been presented in this report.

The first patient showed a complete recovery both clinically and serologically. The second patient still evidenced continued activity after a year. The third patient had a chronic adhesive pericarditis at necropsy. The microscopic appearance was that of a granulomatous process indistinguishable morphologically from tuberculosis. The diagnosis rested on the identification of spherules in the lung and in a giant cell in the pericardium, as well as the exclusion of tuberculosis by a negative skin test, negative sputum studies, and negative stains of the pathologic material.

All three patients had negative tuberculin skin tests and positive coccidioidin sensitivity. The coccidioidal serology was positive in two cases and was not determined in the third, because the diagnosis was not recognized until after necropsy. In the two patients who had sputum studies no tubercle bacilli were recovered on smear, culture or guinea pig inoculation.

All three showed roentgenologic evidence of pulmonary disease. This ranged from a frank pneumonitis with rapid clearing in the first to a chronic pulmonary fibrosis in the third.

The electrocardiographic findings were classical for pericarditis in one, compatible with pericarditis in a second and entirely nonspecific in the third. No marked pericardial effusion, so often seen in tuberculosis, was observed in any of these three patients. The necropsy findings on one make it clear that structural changes can be produced in the pericardium which might ultimately embarrass cardiac function and lead to a Pick's syndrome. Two of the patients were mistakenly diagnosed at some time in their course as myocardial infarction.

It is believed that coccidioidal pericarditis must be considered in the differential diagnosis of any patient living in or having visited an endemic area who presents the picture of pericarditis or myocardial infarction. This diagnosis may be strengthened by the finding of a coincident pneumonitis on x-ray study and a positive coccidioidin skin test. The ultimate diagnosis rests on positive coccidioidal complement fixation and precipitin tests or recovery of the organism from the sputum.

Sumario Español

En areas endémicas donde la coccidioidomicosis se encuentra, pericarditis de etiología obscura merece una investigación para coccidioidomicosis. Una prueba de piel para coccidioidomicosis es de valor. Para establecer el diagnóstico, sin embargo, se depende de una prueba de fijación de complemento y una prueba de precipitación, o recobro del organismo del esputo o el fluído pericardíaco.

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Alterations of the Lesions of Acute Rheumatic Myocarditis during Cortisone Therapy

By ABNER GOLDEN, M.D., AND JOHN WILLIS HURST, M.D.

The changes in the cardiac lesions of a patient dying with acute rheumatic heart disease treated with cortisone are reported. The findings indicate that the effect of this hormone upon the lesions consists in an inhibition of the inflammatory reaction without demonstrable alteration of the collagen injury.

FINAL evaluation of the therapeutic effectiveness of adrenocorticotropic hormone (ACTH) and cortisone in acute rheumatic fever must be based on alterations produced by these agents in the morphologic manifestations of the disease. We have recently observed such alterations in a patient dying with an acute exacerbation of rheumatic myocarditis who received cortisone therapy during the last 15 days of life. The changes in the acute myocardial lesions were characterized by a striking lack of inflammatory cellular response to extensive interstitial collagen degeneration. This change was confined to recent lesions; older, healing lesions appeared unaltered.

The administration of adrenocorticotropic hormone or cortisone to patients suffering from acute rheumatic fever with carditis is often associated with dramatic clinical improvement; at times it appears to be life saving. The significance of this clinical response in terms of any true alteration of the long-term course of the illness cannot as yet be ascertained. Many years of study will be required to determine if permanent damage to the heart valves and myocardium has been prevented or measurably reduced. Morphologic observations during the acute phase of illness thus assume importance and warrant detailed description.

REPORT OF CASE*

J. J., a 10 year old white female, was admitted to the Emory University Hospital on March 21, 1952. She had been well until September 1951, at which time she complained of stiffness and soreness of her legs not associated with joint redness or swelling. On Nov. 15, 1951, the patient complained of a sore throat. Two weeks later, she hurt her hip and two days after this noted swelling of both knees and ankles. One of the knees became red and tender. She was seen by her local physician on Dec. 1, 1951, who found her acutely ill with a temperature of 101 F., markedly dyspneic and slightly cyanotic. There was sinus tachycardia at a rate of 120 per minute with occasional extrasystoles. Two days later, cardiac dilatation and a gallop rhythm were noted. She was admitted to another hospital and was digitalized. She was placed on adrenocorticotropic hormone (ACTH), 10 mg. four times a day, for one day, and then 20 mg. twice daily until dismissal from the hospital. For several days large doses of penicillin were given. Oxygen was administered and she was sedated. She was placed on a salt free liquid diet and was given 250 cc. whole blood on two successive days. By Dec. 21, 1951, she had improved sufficiently to be discharged to home care. She was now given 25 mg. cortisone orally four times daily until Jan. 3, 1952. During the next two weeks she received 25 mg. of cortisone twice a day and for the subsequent two weeks 25 mg. per day. Cortisone was discontinued on Feb. 2, 1952. During this six weeks period she had been kept at absolute bed rest and was given .05 mg. digitoxin daily. She also received 0.6 Gm. sodium salicylate twice daily which was reduced to 0.6 Gm. daily for the following month.

On March 15, 1952, the patient became extremely dyspneic and developed severe cough. She was unable to retain food and medication. Two days later she was again hospitalized and intranasal oxygen was administered. She was placed on 25 mg. of cortisone every six hours and digitoxin was given intravenously. She was transferred to Emory University Hospital March 21, 1952.

At the time of admission to this hospital, the patient was critically ill, markedly dyspneic, pale and emaciated. Her rectal temperature was 100 F. The extremities were cool and the lips and finger tips

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were cyanotic. The entire chest and body rocked with each heart beat. The cardiac apex was in the left mid-axillary line and auricular fibrillation was present, with an uncontrolled ventricular rate of 180 per minute. There was a grade 3 systolic murmur and a grade 2 diastolic rumble at the apex. A grade 1 systolic murmur was heard in the pulmonic valve area. Examination of the lungs revealed numerous coarse bubbling rales and wheezing over both lungs. The respiratory rate was 60 per minute. The blood pressure was 120/75. Femoral artery pulsations were normal and there was no peripheral edema. The liver was palpated 5 cm. below the right costal margin but the spleen was not palpable. No petechiae were found.

The red blood cell count was 4,500,000 per cubic millimeter and the blood hemoglobin content was 12.6 Gm. per 100 cc. The blood sedimentation rate (Westergren) was 50 mm. in one hour. The white blood cell count was 18,700 per cubic millimeter, with 77 per cent neutrophiles, 6 per cent band forms, 1 per cent eosinophils, 2 per cent metamyelocytes and 14 per cent lymphocytes. The specific gravity of the urine was 1.026 and the pH was 5.0. The test for sugar was 2 plus (after subcutaneous glucose with Allidase); there was no albumin. The sediment was not remarkable. A repeat urinalysis five days later showed no significant change except for 1 plus albuminuria and a trace of sugar. The blood Kahn test was negative. On March 22, 1952, the blood nonprotein nitrogen was 58 mg. per 100 cc. and the carbon dioxide combining power was 25 mEq. per liter. The serum chloride was 94.8 mEq. per liter and the serum sodium and potassium were 137.2 and 3.9 mEq. per liter, respectively. Four days later, the nonprotein nitrogen was 44 mg. per 100 cc., the carbon dioxide combining power was 29 mEq. per liter and the serum chloride was 95 mEq. per liter. The serum sodium and potassium were 131 and 5.0 mEq. per liter, respectively. Three blood cultures yielded no growth.

An electrocardiogram showed auricular fibrillation, with an uncontrolled ventricular rate of 160. There was moderate right axis deviation and evidence of digitalis effect. X-ray examination of the chest showed marked generalized cardiac enlargement. The diaphragmatic leaves were poorly outlined because there was fluid in both pleural cavities. There was extensive, poorly demarcated, consolidation throughout both lung fields.

Course in Hospital

At the time of admission the patient was given 20 mg. of Demerol intramuscularly and nasal oxygen. She received 0.6 mg. of lanatoside C intramuscularly in an attempt to control the ventricular rate. Mercuhydrin (1 cc.) was given intramuscularly and 0.18 Gm. aminophyllin was given intravenously. Tourniquets were applied to the extremities. During the next several hours dyspnea lessened and the ventricular rate slowed to 140.

The day after admission, the patient was started on 100 mg. of cortisone intramuscularly every eight hours. This dosage was continued until the patient died, at which time she had received a total of 3,200 mg. Her temperature gradually rose, reaching 105.6 F. on the fourth hospital day. She was started on 300,000 units of procaine penicillin intramuscularly every eight hours, and 0.6 Gm. acetyl salicylic acid every four hours. Within two days the temperature had declined to 102 F. but she continued to run a low grade fever of 100 to 101 F. until death. Demerol, mercurial diuretics, aminophyllin and intramuscular lanatoside C were used in an attempt to control her congestive heart failure and severe dyspnea. Her ventricular rate remained uncontrolled. Hydration was maintained by the administration of 500 cc. of 5 per cent glucose in water at frequent intervals, with 0.5 to 1.0 Gm. of potassium chloride added on several occasions. The patient continued to have periodic episodes of pulmonary edema.

A fecal impaction became obvious on March 29, 1952, despite the fact that she had had occasional bowel movements. It was impossible manually to reach the area of impaction and frequent oil enemas were unsuccessful. The abdomen became distended and the patient became moribund. The cardiac rhythm became completely regular with a ventricular rate of 180 per minute. She died shortly thereafter, with evidence of ventricular tachycardia and fibrillation, on the eleventh hospital day.

Pathologic Findings

Autopsy was performed two and one-half hours post mortem. The body was that of a poorly nourished white girl measuring 130 cm. in length. There was slight enlargement of the right knee joint. Both pleural cavities contained 50 cc. of clear, straw colored fluid. No free fluid was present in the peritoneal cavity and there was no dependent edema.

The pericardial cavity was partially obliterated by dense, fibrous adhesions. Other areas displayed a shaggy appearance with a few loose fibrinous adhesions between visceral and parietal pericardium. No free fluid was present. The heart weighed 350 Gm. (normal weight 116 Gm.) All cardiac chambers were dilated. The mural endocardium of the left and, to a lesser degree, the right atrium appeared thickened and opaque. The valve measurements were: tricuspid valve 11.0 cm.; pulmonic valve 5.2 cm.; mitral valve 12.0 cm.; aortic valve 5.0 cm. Both cusps of the mitral valve were moderately thickened, and their chordae tendineae were shortened and frequently fused. The cusps of the tricuspid valve were slightly thickened and opaque, and there was questionable fusion of adjacent aortic valve leaflets. The pulmonic valve appeared normal. No vegetations were seen anywhere. The myo-

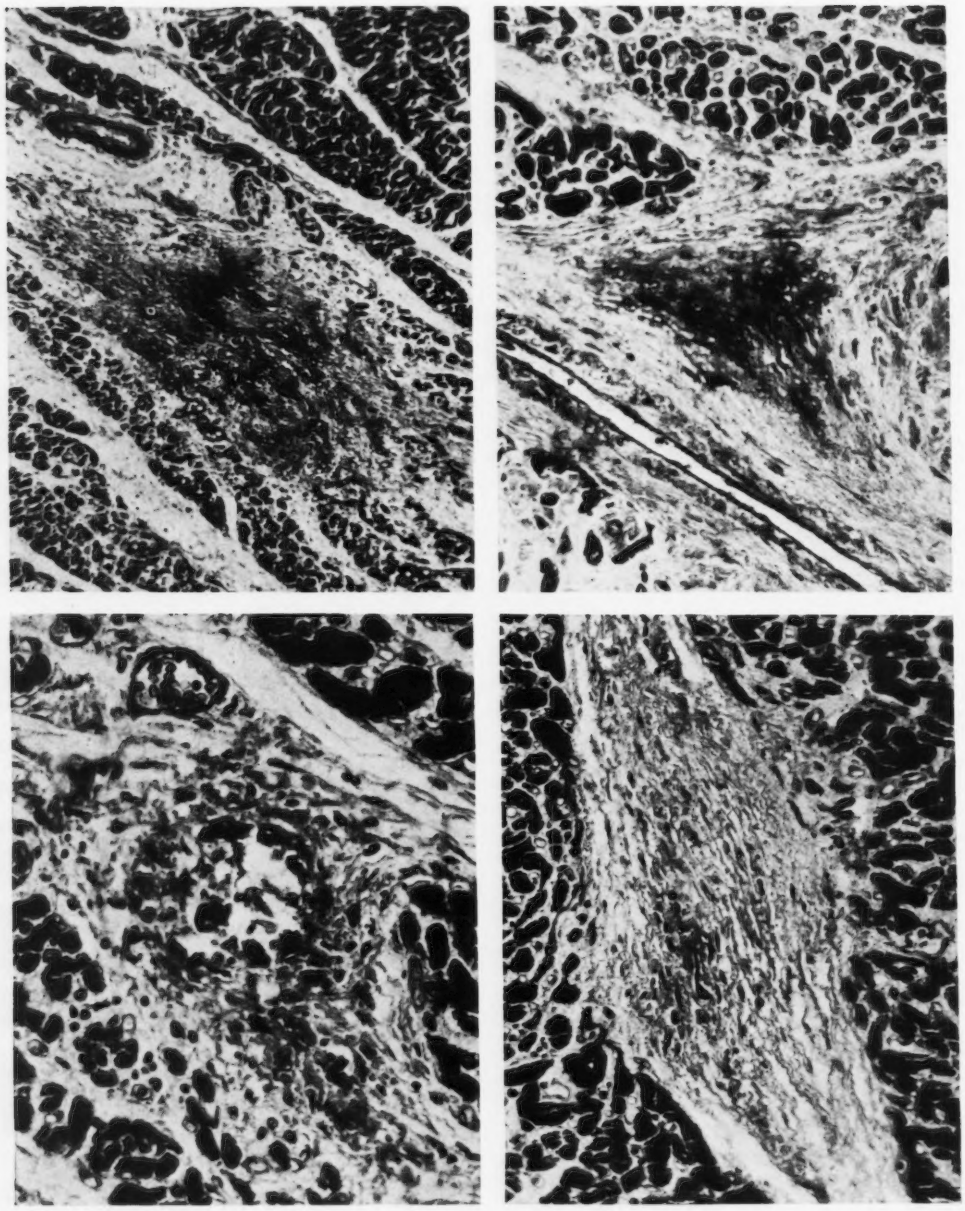

FIG. 1. (*top left*) Myocardium. A large area of recent fibrinoid degeneration in the interstitial connective tissue. Hematoxylin and phloxine ×90.

FIG. 2. (*top right*) Myocardium. Acute fibrinoid degeneration of interstitial connective tissue. Note the absence of inflammatory response. Hematoxylin and phloxine ×210.

FIG. 3. (*bottom left*) A myocardial Aschoff nodule of some duration. Aschoff cells and fibroblastic proliferation are present. Hematoxylin and phloxine ×400.

FIG. 4. (*bottom right*) Older myocardial lesion showing almost complete fibrosis. A few Aschoff cells are still seen. Hematoxylin and phloxine ×210.

cardium of the left ventricle measured 1.8 cm., that of the right ventricle 0.5 cm. The myocardium was flabby in consistency and pale, grayish brown in color without focal lesions.

The left lung weighed 200 Gm., the right 610 Gm. The bronchi contained a moderate amount of pink, frothy fluid. Scattered throughout both lungs were many large, confluent and ill-defined areas that were firm in consistency and appeared hemorrhagic. No thrombi were present in the branches of the pulmonary artery.

The combined weight of the adrenal glands was 9.1 Gm. There was a fecal impaction of the sigmoid colon. With the exception of passive congestion, no abnormalities were noted in the spleen, pancreas, kidneys, pelvic organs, great vessels, lymphatic tissue or bone marrow. Permission was not granted for examination of the extremities or the brain.

Tissues were fixed in Zenker's fluid with 5 per cent glacial acetic acid and in 10 per cent formalin, USP. Histologic sections were stained routinely with hematoxylin and phyloxine. Selected sections were prepared with phloxine-methylene blue, Mallory's phosphotungstic acid-hematoxylin, the Gram-Weigert stain for fibrin, and the periodic acid-Schiff technique.

The myocardium revealed numerous interstitial lesions many of which were acute and of highly atypical appearance (figs. 1, 2). They consisted of varying sized, but frequently extensive and stellate areas of intense fibrinoid degeneration of collagen accompanied by little or no cellular reaction. Large mononuclear cells of the Aschoff type were completely absent, but an occasional small "myocyte" was present at the periphery of a few of these lesions. Adjacent myocardial muscle fibers appeared uninjured. This lack of cellular reaction was a striking finding in view of the large number and size of the lesions encountered.

Other myocardial lesions appeared to have been present for some time, and showed varying stages of healing (figs. 3, 4). Many revealed early proliferation of fibroblasts and contained the usual complement of large mononuclear Aschoff cells and Anitschkow myocytes (fig. 3). The oldest lesions appeared to consist of perivascular areas of dense fibrosis. None of the healing lesions appeared to differ significantly from those encountered in rheumatic myocarditis not treated with ACTH or cortisone. The only other finding in the myocardium was a slight patchy perivascular infiltration of small lymphocytes and plasma cells and an occasional polymorphonuclear leukocyte. There was no evidence of active rheumatic arteritis.

Sections of pericardium revealed a pericarditis showing generally advanced healing. A few areas of lymphocytic and plasma cell infiltration were seen, but no acute lesions were encountered. The endocardium of the left atrium showed an extensive area of mural endocarditis in advanced repair. The mitral valve cusps contained an increase in fibrous connective tissue and were partially vascularized. Arterioles in the valve ring area demonstrated a concentric thickening and scarring of their walls. An occasional minute area of valvular endocarditis was noted near the attachment of the chordae tendineae, consisting of slight disruption of the endothelial surface and surrounding proliferation of connective tissue elements. These lesions also appeared to be of considerable standing. The tricuspid valve displayed minimal thickening by fibrous connective tissue and slight vascularization.

The lungs revealed an extensive passive congestion and patchy edema. In some areas, the alveolar septa were thickened by fibrous tissue. Other areas showed focal fibrinoid necrosis of septa with alveolar hemorrhage and fibrin deposition simulating the appearance of an asphyxial membrane. Many deposits of fibrin were undergoing organization and others were completely replaced by fibrous tissue. The recent changes in the alveolar septa were associated with a moderate interstitial infiltration of mononuclear phagocytes and lymphocytes and occasionally polymorphonuclear leukocytes. No abnormalities were noted in branches of the pulmonary arteries.

The adrenal glands revealed a marked cortical atrophy, involving principally the zona fasciculata. A moderate degree of medial cystic necrosis was encountered in the aorta. Sections of the spleen, pancreas, liver, kidneys, lymph nodes and bone marrow were not remarkable except for passive congestion.

Anatomic Diagnoses. Rheumatic heart disease, acute and chronic, with pericarditis, endocarditis and massive myocarditis; cardiac hypertrophy (350 Gm.); rheumatic pneumonitis; passive congestion of viscera; pleural effusion, bilateral; adrenal cortical atrophy; medial cystic necrosis of aorta; fecal impaction.

Discussion

The patient, a 10 year old girl, first manifested definite clinical evidence of acute rheumatic fever in September, 1951, six months before her death. Her course indicated constant and progressive activity of her disease. Early in her illness, she was treated with prolonged courses of adrenocorticotropic hormone (ACTH) and cortisone. She received no hormone therapy for a six weeks period terminating 16 days before death. During her final hospitalization, she was given large doses (100 mg. every eight hours) of cortisone. There was no demonstrable clinical response to this therapy, and she died of intractable congestive heart failure.

The most striking finding at autopsy was a rheumatic myocarditis of atypical appearance. Acute, as well as older lesions in various stages of repair, were seen. The acute lesions consisted of extensive areas of interstitial fibrinoid degeneration of collagen, but there was remarkably little or no cellular reaction. Large mononuclear Aschoff cells were completely absent. The presence of healed and healing myocardial, valvular and epicardial lesions corresponded with the prolonged and "smoldering" clinical course. None of the older healing lesions differed significantly from those seen in rheumatic carditis not treated with adrenocorticotropic hormone or cortisone. An extensive rheumatic pneumonitis similarly revealed no alteration in cellular reaction.

Although many authors have postulated that the dramatic clinical response of acute rheumatic heart disease under adrenocorticotropic hormone or cortisone therapy is based on inhibition of the inflammatory component of cardiac lesions, morphologic observations, although few, have not supported this concept. The reports of Spain,[1] Smith,[2] and Rosenblum[3] indicate no histologic alterations in the characteristic lesions of rheumatic fever. Massell and Warren[4] noted the absence of acute cardiac lesions in a patient treated for three months for rheumatic fever with adrenocorticotropic hormone and dying with jugular thrombophlebitis.

Our findings are similar to those encountered by Bunim[5] in subcutaneous rheumatic nodules during cortisone therapy. His text figure 8 shows a large mass of fibrinoid necrosis of collagen devoid of cellular reaction.

The lesions we have observed may be interpreted as representing a suppression of cellular reaction to altered collagen. This interpretation is in accord with the experimental observations of others,[6, 7, 8] showing a quantitative inhibition by adrenocorticotropic hormone and cortisone of inflammatory cell reaction to tissue hypersensitivity reactions.

Our findings do not indicate that the injury to connective tissue associated with rheumatic fever has been prevented to any degree. Experimental observations suggest that a quantitative reduction in the number of cardiac lesions may occur during hormone administration. Bennett, Berthrong and Rich[9] were able, in most instances, to prevent the formation of myocardial lesions associated with anaphylactic hypersensitivity in rabbits by the administration of either adrenocorticotropic hormone or cortisone. Most clinical evidence, however, indicates that acute rheumatic fever runs its natural course whether or not its manifestations are suppressed by hormone therapy.[5]

We are unable to evaluate the effect of the morphologic alterations we have observed on the eventual fate of the lesions. Our patient received adrenocorticotropic hormone and cortisone early in her illness, but no change was apparent in the older myocardial lesions. They differed in no way from those seen in rheumatic myocarditis not treated with these hormones. Experimental observations suggest that withdrawal of hormone therapy may be quickly followed by an inflammatory cell infiltration into areas of collagen degeneration and the usual sequence of healing.[10] Prolonged suppression of inflammatory reaction, however, might result in decreased scar tissue formation when final healing has occurred. The significance of our observations will have to be determined by the long-term studies now in progress of patients with rheumatic heart disease who have been treated successfully with adrenocorticotropic hormone and cortisone.

Summary

Morphologic alterations were observed in the lesions of acute rheumatic myocarditis in a patient receiving large doses of cortisone. The changes consisted of a striking lack of cellular reaction to extensive interstitial collagen degeneration. Myocardial lesions which appeared to be of longer duration displayed varying degrees of healing and did not differ from those seen in rheumatic myocarditis not treated with adrenocorticotropic hormone or cortisone.

Sumario Español

Los cambios en las lesiones cardíacas en un paciente que muere con una carditis reumática

tratado con cortisona se reportan. Los cambios indican que el efecto de la hormona en los tejidos consiste en una inhibición de la reacción inflamatoria sin alteración demostrable del daño colágeno.

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Effect of Cortisone on the Size of Experimentally Produced Myocardial Infarcts

By Aran S. Johnson, M.D., Schayel R. Scheinberg, M.D., Robert A. Gerisch, M.D., and Harry C. Saltzstein, M.D.

In a total of 57 dogs the anterior descending branch of the left coronary artery was doubly ligated. Cortisone apparently (1) reduced the area of residual fibrosis; (2) increased the vascularity of the heart.

EXPERIMENTALLY produced myocardial infarcts in dogs, treated with cortisone, have shown a much smaller area of residual fibrosis than untreated infarcts in the control animals. The idea for this work developed when one of us (A. S. J.) was evaluating the effect of pericoronary neuronectomy on revascularization of the myocardium following experimentally produced myocardial infarction in dogs. The results of the latter experiments were obscured by massive pleural and pericardial adhesions. Hence, since previous work[1] had shown that cortisone decreased the formation of abdominal adhesions, it was thought that cortisone might also reduce pleural and pericardial adhesions. The animals treated with cortisone showed not only a decrease in pleural and pericardial adhesions, but also had a much smaller area of residual fibrosis in the myocardium. With these findings in mind the present study was undertaken.

Procedure

Mongrel dogs weighing 25 to 45 pounds were anesthetized with intravenous sodium Nembutal (1 cc. per 5 pounds). Pressure oxygen was given through an endotracheal tube. The heart was exposed by a left thoracotomy incision with removal of a segment of the fourth rib. The pericardium was opened and the anterior descending branch of the left coronary artery was doubly ligated with triple O silk.

The animals were divided into three groups. In group I (14 animals), the anterior descending branch of the left coronary artery was ligated 1.5 cm. below the origin of the circumflex branch (low ligation). Seven of these animals were treated with cortisone in doses of 12.5 mg. to 20 mg. twice daily for 14 to 22 days and seven animals were kept as controls. All animals were sacrificed 14 to 22 days after operation.

In group II (18 animals), the anterior descending branch of the left coronary artery was ligated 0.5 cm. below the origin of the circumflex branch (high ligation). Nine animals were treated with cortisone, 20 mg. twice a day for 20 days, and nine animals were kept as controls. All of these animals were sacrificed 30 days after operation. They had been confined to their cages until the time of sacrifice and had received 1 cc. of procaine penicillin (300,000 units) daily postoperatively for four days.

Cortisone used in these experiments was given intramuscularly and the initial dose was given immediately as the coronary artery was ligated. Electrocardiograms (standard limb leads, augmented unipolar leads and V leads) were taken before, during and after ligation of the coronary artery.

Upon sacrifice of the animals the heart and lungs were exposed and photographed in-situ. Then the heart and lungs were removed en bloc. The hearts were studied by means of x-ray films of the injected coronary bed by the following technic: The right and left coronary arteries were isolated and a cannula was introduced into these vessels and tied. A 20 per cent suspension of bismuth oxychloride with a 20 per cent gum acacia base was injected through the cannula under pressure varying from 80 to 120 mm. Hg.[2] X-ray films were then taken of the heart (fig. 1).

After injection, the hearts of all coronary ligated animals were fixed in 10 per cent formaldehyde for three days and then sectioned serially. The length, width and depth of the infarcted area was measured by calipers and centimeter rule. Sections were taken for microscopic study.

Group III included a series of 12 dogs in which no operation was performed. Four animals received cortisone, 50 mg. daily for two months, and four

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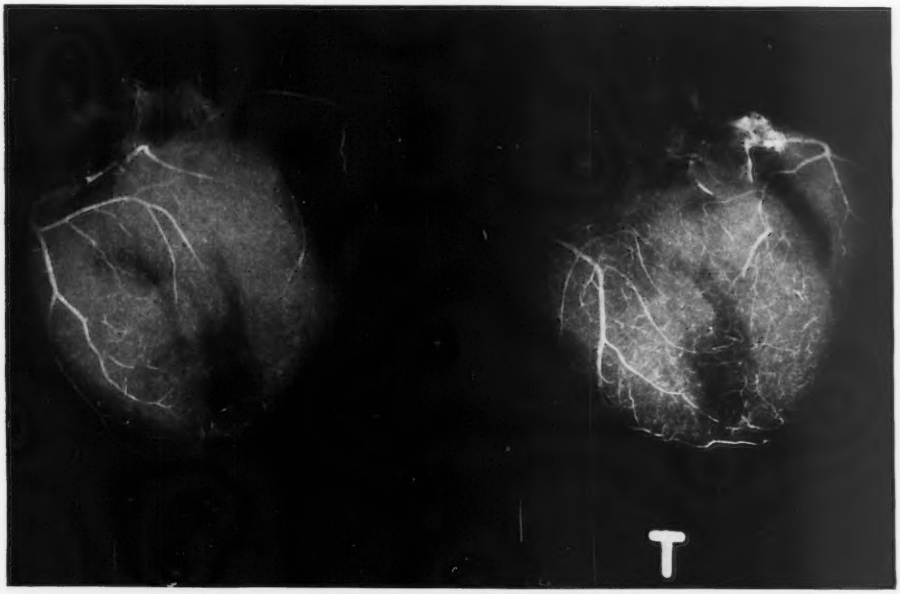
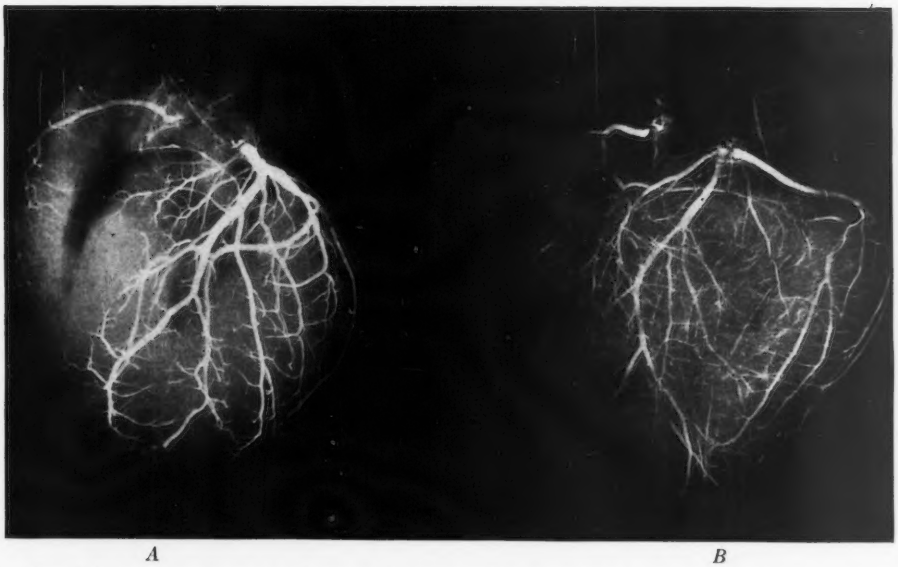
Aided by grants from Merck and Co., who also supplied the cortisone, and from The National Foundation of Rochester, Michigan; and The Michigan Heart Association.



A *B*

Fig. 1. X-ray-injection study of treated (A) and control (B) animals of group I.



A *B*

Fig. 2. X-ray-injection study of control (A) and treated (B) animals of group III who received cortisone.

received adrenocorticotropic hormone, (ACTH) 30 mg., daily for two months. The four remaining animals were kept as controls. At the end of two months all animals were sacrificed and injection studies of the hearts were made (fig. 2).

Results

The results in group I and group II are presented in tables 1 and 2 respectively. Grossly, the myocardial infarcts in the cortisone-treated

animals were much smaller than those in the control group.

In group I, low ligation, the average size of the infarct in the seven control animals expressed in cubic centimeters was 7.28, whereas that in the treated animals was only 0.96 cc. (table 1). In the treated animal of pair 6, the size of the infarct was 4.8 cc. This treated dog failed to receive cortisone for two days—from the fourth to sixth postoperative day. In all other treated animals the infarct was less than 1.0 cc.

TABLE 1.—*A Summary of Findings in Animals of Group I (Low Ligation)*

Dogs in Parallel Series of Two	Control			Treated Cortisone for 14 days (I.M.)		
	Wt. of dog in lbs.	Wt. of heart in grams	Size of infarction in cubic cm.	Wt. of dog in lbs.	Wt. of heart in grams	Size of infarction in cubic cm.
1	30	123	4.20	35	120	0.80
2	37	125	5.63	33	115	0.20
3	23	80	2.0	30	100	0.20
4	26	80	5.4	25	78	0.45
5	25	90	11.25	32	110	0.002
6	20	80	13.5	30	115	4.8
7	50	150	9.0	45	130	0.27
Average	30	104	7.28	32.9	109	0.960

TABLE 2.—*A Summary of Findings in Animals of Group II (High Ligation)*

Dogs in Parallel Series of Two	Control			Treated Cortisone for 20 days (I.M.)		
	Wt. of dog in lbs.	Wt. of heart in grams	Size of infarction in cubic cm.	Wt. of dog in lbs.	Wt. of heart in grams	Size of infarction in cubic cm.
1	30	110	15.20	32	110	0.50
2	45	132	22.75	45	134	0.10
3	40	130	22.75	35	130	0.22
4	32	105	27.00	36	125	0.20
5	35	125	12.95	35	120	0.00
6	30	110	19.50	30	120	0.25
7	34	105	15.40	36	100	0.00
8	40	120	20.50	42	115	0.00
9	25	80	13.50	29	80	0.00
Average	35.8	117.1	18.83	36.2	119.2	0.141

In group II, high ligation, the average size of the infarct in the nine control animals expressed in cubic centimeters was 18.83, while that in the treated animals was only 0.141 (table 2). In the control animals of group II all infarcts measured more than 12 cc. whereas in the treated animals the infarcts were less than 1.0 cc. In four of the treated animals no residual fibrosis could be seen on the gross specimen.

Figure 1 demonstrates a comparison of the coronary circulation in the treated (A) and control (B) animals by means of x-ray injection technic. All hearts in groups I and II were studied in this way. Very marked differences were apparent in the two groups. The control animals showed very little or no interarterial coronary anastomosis in the infarcted area whereas in the treated animals there was an apparent increase in blood supply to the area involved.

The animals in group III, which were treated with cortisone and adrenocorticotropic hormone (ACTH) but did not have an experimentally produced myocardial infarct, revealed a more prominent vascular pattern, both on gross inspection and on the injection study, than the control animals (figs. 2 and 3). It was also noted that the dye injected into the left coronary artery promptly appeared in the right coronary artery and its branches, which was not observed in the hearts of the control animals.

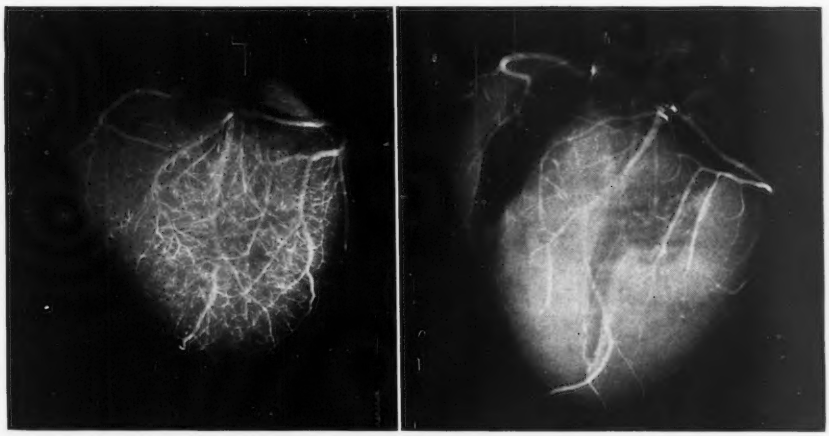
Two pairs of animals (two controls and two treated) were sacrificed 72 hours after operation. There was a decided difference in the coronary vessels and the area of infarction. The control animals showed large infarcts with absence of collateral branches. The cortisone-treated animals, on the other hand, showed minimal infarcts and numerous collateral branches coursing through an area comparable to the infarcted area in the control animal.

Complete and detailed electrocardiographic findings will be reported at a future date. Suffice it to say at this time that in animals on which coronary ligation was performed, both treated and control, the electrocardiograms showed patterns consistent with an acute myocardial infarction.

Table 3 gives the postoperative mortality. In the control series, there were 34 animals and 18 deaths. This is a mortality of 52.9 per cent. Thirteen of these deaths occurred within one half hour after operation. In the cortisone-

treated series, there were 23 animals and five deaths. This is a mortality of only 21.5 per cent.

Histopathologic observations revealed that cortisone produces a marked decrease in local fibroblastic proliferation during the first 14 days of healing of the infarct. These changes are manifested chiefly at the edge of the area of necrosis. In the treated animal there is a sharp line of demarcation between the area of infarction and adjacent muscle, whereas the control shows a broad, irregular zone of healing. The muscle surrounding the infarcted area in the treated animal takes the stain better than the corresponding muscle tissue in the control animal. These histologic distinctions are no longer apparent after 30 days.



A *B*

Fig. 3. X-ray-injection study of treated (A) and control (B) animals of group III who received adrenocorticotropic hormone (ACTH)

TABLE 3.—*Animal Mortality Rate on Total Number of Dogs up to Date*

	Total Number of Dogs Operated	Time of Death Postoperative						
		15 Min.	30 Min.	12–14 Hrs.	24–36 Hrs.	48 Hrs.	72–96 Hrs.	Total Deaths
Control	34	2	11	2	1	1	1	18 or 53 %
Treated (cortisone)	23	1	2	1	0	0	1	5 or 22 %

Discussion

It would seem that we are dealing here with two distinct effects of cortisone on the myocardium. The marked decrease in local fibroblastic proliferation during the early stages of healing of the infarcted area in the cortisone-treated animals is consistent with repeated observations of the effect of cortisone on all mesenchymal tissues. Many workers have demonstrated that cortisone produces delay in fibrosis, diminished cellular reaction, scanty formation of ground substance, little capillary formation and complete lack of fibrin and exudate.[3] This phenomenon is no doubt in part responsible for the marked absence of adhesions in the abdomen, chest, and pericardium in cortisone-treated animals.

A second effect which, so far as we know, has not been described heretofore, is the direct action of cortisone on the entire vascular system of the heart. The existence of interarterial coronary anastomoses in mammalian hearts has been generally accepted.[4] Our injection arteriograms show increased interarterial anastomoses in the cortisone-treated animals. These were present in both the coronary ligated and the noncoronary ligated animals which received cortisone. This effect was apparently sufficient to decrease the area of residual fibrosis.

It should be pointed out that Chapman and

co-workers have studied the effect of cortisone in experimentally produced myocardial infarction with interest in healing of the infarcted area and electrolyte changes.[5] They report that cortisone given to dogs with experimentally produced myocardial infarcts produced no deleterious effects either on the size of the infarcts or on the rate or quality of myocardial healing. They also report that no significant disturbance in electrolyte balance occurred.

Since this work has numerous clinical inferences, further investigative work is being done. It must be remembered that complications of cortisone and adrenocorticotropic hormone therapy which have been reported include sodium and water retention, elevation of blood pressure, and an increased tendency toward thromboses. Moreover it is not known whether the action of cortisone and adrenocorticotropic hormone in dogs can be considered to have the same effect in man. Hence, until further work is completed in regard to dosage, time of administration, and duration of treatment this work must be considered purely experimental. It can be said however that in the entire series of treated animals there were no untoward effects such as rupture of the myocardium or aneurysmal dilatation which might be ascribed to delay in healing. A preliminary report of this work was published in December, 1951.[6]

Conclusions

1. In myocardial infarcts experimentally produced by low coronary ligation, the average size of the infarcts in the cortisone-treated animals was 0.96 cc., whereas in the control animal the average size of the infarct was 7.28 cc.

When the infarct was produced by high coronary ligation, the average size of the infarcts in the cortisone-treated animals was 0.141 cc. whereas in the control animal the average size of the infarcts was 18.83 cc.

2. The mortality in the control animals was 52.9 per cent whereas in the treated animals it was only 21.5 per cent.

It is apparent that after an acute coronary occlusion, animals receiving cortisone have a 25 per cent better chance of survival.

3. The local area of infarction showed a marked decrease in local fibroblastic proliferation and a delay in healing during the early stages in the cortisone-treated animal.

4. Cortisone also produced a general effect on the heart. Postmortem injection studies demonstrated increased interarterial coronary anastomoses throughout the vascular system of the heart. We believe that this provided sufficient collateral circulation to lessen the area of infarction.

5. Postmortem injection studies also revealed increased interarterial coronary anastomoses in the hearts of dogs receiving cortisone and adrenocorticotropic hormone without ligation of the coronary arteries.

Acknowledgments

We wish to thank the following for their continued interest and help in this work: Dr. Lawrence Reynolds and the Department of Radiology; Dr. Hugo A. Freund; Drs. Plinn F. Morse, William L. Brosius, and Fred W. Girton of the Department of Pathology; Dr. Edward D. Spalding and the Department of Cardiology; and Virginia J. DeBruin, R.N., for her invaluable technical assistance.

Sumario Español

En un total de 57 perros la rama anterior descendente de la arteria coronaria izquierda fué ligada doblemente. Cortisona aparentemente (1) redujo el area de fibrosis residua; (2) aumentó la vascularidad del corazón.

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Ballistocardiography

I. Physical Considerations

By MAURICE B. RAPPAPORT, E.E., HOWARD B. SPRAGUE, M.D., AND WILLIAM B. THOMPSON, M.D.

A physical analysis is presented of the Starr, Nickerson, and Dock methods for registering the ballistocardiogram. It is shown that many forms of distortion are present. Some of the distortion may be present in the instrumentation which may be controlled, and other forms of distortion are inherent in the subject under test which are most difficult to control or evaluate. The effects which some of the uncontrollable variables have upon the amplitudes and temporal positioning of the registered ballistocardiographic waves is analyzed. The status of static and dynamic standardization procedures is discussed. A "Glossary of Technical Terms" is appended.

CONSIDERABLE confusion exists at the present time in ballistocardiography with regard to the instrumental aspect as well as the clinical interpretation of the graph. Ballistocardiographs are in use which definitely do not register identical records on the same individual and their modes of distortion are multitudinous. The purpose of this analysis and investigation is to determine and illustrate the common forms of distortion which may be introduced by instrumentation and technic and then proceed to analyze the component waves in the normal subject by simultaneously registering the ballistocardiogram with other physiologic events.

A ballistocardiogram is a graphic representation with respect to time of the motions which are imparted to the body in response to the physical movements of the heart, the ejection of blood from the heart, and the passage of the blood through the vascular system. The ballistic movements of the body as a result of cardiac action follow in principle Newton's third law of motion which states that "to every action there must be an equal and opposite reaction." The ballistic force vector which imparts the movement to the body is of variable magnitude throughout the cardiac cycle and its spatial direction changes. Furthermore, the magnitude and direction of the instantaneous spatial force vector is not necessarily equal in two normal subjects at the same instant during the cardiac cycle because of dissimilarity in anatomic positioning and the forcefulness of cardiac activity. The amount of movement imparted to the body is in turn dependent upon factors such as the compliance of the tissues between the heart and the skeletal structure, the compliance of tissues between the vascular system and the skeletal structure, the compliance of the various skeletal joints, the mode of support of the body, the compliance of the tissue between the skeletal structure and the support, and the elasticity and peripheral resistance of the vascular system.

The ballistocardiograph, in its most common form is capable of measuring the ballistic movements of the body axially only—along a line drawn from head to foot which gives the instrument one degree of freedom. The ballistic forces that exist in the body are spatial, therefore, the common forms of ballistocardiographs such as the Starr,[1] Nickerson,[2] and Dock,[3] merely register the body movements which are produced by the projection of the instantaneous spatial vector along the head-foot axis; the projected instantaneous vector is of a lesser magnitude than the spatial vector and the body moves a lesser amount axially than in the direction of the instantaneous spatial vector. This phenomenon has been appreciated by various investigators who have constructed ballistocardiographs which are capable of registration with more than one degree of freedom,[4–8] as, for example, head to foot, back to front and side to side movement. When a ballistocardiograph which is

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capable of measuring body movement with three degrees of freedom is used, the instantaneous spatial vector magnitude and direction may be determined.

Another ballistic factor which has been appreciated is that the spatial force vector is altered by body position. As a result, ballistocardiographs capable of registering with the subject in a standing position,[9–11] instead of the usual supine position, have been constructed; Wilkins[12] devised a tilting table so that positions between supine and standing were additionally obtainable.

The utility of a ballistocardiograph capable of three degrees of freedom for clinical investigation is apparent; however, the complexity of such an apparatus is great. In addition, a complex system of transducers for detecting

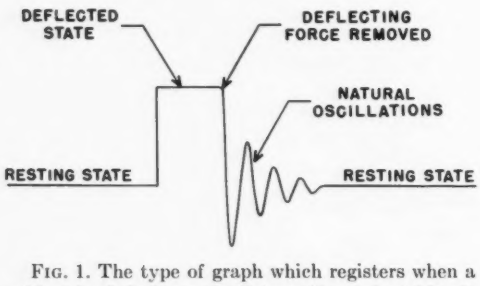

FIG. 1. The type of graph which registers when a subject-loaded Starr ballistocardiograph table is deflected and suddenly released.

head to foot, back to front, and side to side motions, simultaneously registered with one or two other physiologic events, necessitates a four or five-channel recorder. Calculation is then necessary for evaluating the instantaneous spatial vector magnitudes and directions during the cardiac cycle and plotting the locus of the spatial vectors on a three dimensional graph. Experience has indicated that a ballistocardiograph with one degree of freedom sensitive to head-foot movements is capable of giving considerable information. Furthermore, the physical principles which apply to a ballistocardiographic system with one degree of freedom also apply to a system with three degrees of freedom. For simplicity, therefore, we shall discuss the systems with one degree of freedom.

The three forms of ballistocardiograph most commonly used with one degree of freedom are the high-frequency, undamped table suggested by Starr and co-workers,[1] the low-frequency critically damped table devised by Nickerson and Curtis[2] and the instrument based on the method of Dock and Taubman[3] which does not require a suspended table. Let us first consider the characteristics of the Starr ballistocardiograph and their effects upon the resultant ballistocardiogram.

The instrument is essentially a light platform which is supported by springs so that it may vibrate longitudinally (head to foot) at a natural frequency of about 9 cycles per second when a subject of average weight is placed on it. A heavier subject lowers the natural frequency of vibration somewhat whereas a lighter subject raises the over-all natural frequency. The table is undamped except for incidental damping components that may be present in the structure. Thus, if the table is deflected while supporting the subject or an equivalent mass and the deflection force suddenly released, a curve similar to the one in figure 1 will be registered. When the deflecting force is removed, the system goes into a natural oscillation which diminishes logarithmically until a resting or steady state is reached. The logarithmic decrement is caused by some friction and other incidental damping components in the system. If some damping were not present, a sinusoidal oscillation of fixed amplitude would persist which is a physical impossibility as it would be a form of perpetual motion.

All so-called undamped vibrating systems exhibit the phenomenon shown in figure 1; excellent examples are plucked violin strings, and undamped galvanometers, and plucked reeds. In figure 2 is a family of curves which show the response of a vibration system or ballistocardiograph table for various degrees of damping.* At zero cycles per second, which represents a constant displacement of the

* These curves are representative of vibrating systems and are well described in most textbooks on vibration mechanics.[18, 19] The ballistocardiograph table is a vibrating mechanism which falls into this classification. No accurate method has been devised actually to measure such characteristics of tables, but there is no physical reason for a table to deviate in performance.

table, the per cent response in figure 2 is 100 per cent. For example, zero cycles per second is obtained by dividing the applied frequency of zero cycles per second by the natural frequency of the table and zero divided by any finite number is zero. As the applied frequency is increased, the percentage response will vary as indicated by the family of curves. It is apparent from figure 2 that over a range of frequency from zero to at least 75 per cent of the resonant frequency, a ballistocardiograph table without substantial damping produces a deflection which is progressively increased or magnified above the true value. From a clinical standpoint this means that a ballistic wave or component of one frequency will not register with the same magnitude as another ballistic wave of a different frequency although their magnitudes are identical.

It has been shown by harmonic analysis[7] that normal ballistocardiographic waves possess frequency components at least up to 10 cycles per second. The components above 6 cycles per second may be neglected without severe error according to the authors. However, a similar analysis must be made on various abnormal conditions to determine the upper frequency components that must be registered in order to produce a ballistocardiogram of accurate configuration. If a Starr table which is partially damped and possesses a natural frequency of approximately 9 cycles per second is used for the registration of normal ballistocardiograms, registrations will be made on the sections of the response curves of figure 2 from approximately resonance down to the lowest frequency component in the ballistic movement of the subject. The less the degree of damping present, the steeper will be the response curve with respect to the applied frequency.

It may be seen from figure 2 that if a partially damped table is allowed to have a resonance considerably above the highest harmonic component of the ballistic wave, the response curve will be less steep with respect to frequency. If the natural frequency is made high enough, the working spectrum can be considered flat for all practical purposes. From a theoretic standpoint this would be an excellent procedure, but from a practical standpoint some almost insurmountable obstacles appear. For example, to increase the natural frequency of the table by a considerable amount, extremely stiff springs must be employed and the sensitivity or degree of table movement is reduced inversely as the square of frequency increase. That is, if the natural frequency is doubled, the table movement is reduced fourfold; if the natural frequency is increased tenfold the movement is reduced one hundred times. This obviously places a severe burden upon the detecting and recording systems. Furthermore, as the natural frequency is increased, the degree of damping which is incidental in the Starr table exhibits a lesser effect and a lower degree of damping results.

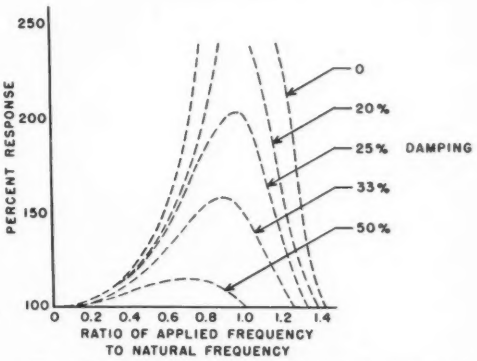

FIG. 2. Family of curves which are characteristic of vibrating systems. The ballistocardiograph which is such a vibrating system may be represented by these curves and the per cent response which results from an applied force at any frequency may be evaluated if the degree of damping is known.

This phenomenon tends to neutralize the gains which would result from an increase in natural frequency.

It is apparent that a Starr table with a natural frequency of approximately 9 cycles per second when loaded with an average subject does have an appreciable frequency response slope. This is readily observed when ballistocardiograms are registered with the subject breathing normally. This table will register the ballistocardiogram with but a minimal superimposed respiratory weave of the base line. When a ballistocardiogram is registered with an instrument which has a flat frequency response characteristic such as will be discussed later, the respiratory weave will

register on the same subject with an amplitude many times the magnitude of the ballistic waves. The average rate of breathing is approximately 20 per minute which corresponds to a breathing frequency of 0.3 cycles per second. An average ballistic frequency of cardiac origin is approximately 5 cycles per second. Thus, a comparison of the graphs taken with the two types of ballistocardiograph will give a rough estimate of the degree of slope of the frequency response curve. It should be mentioned at this time that because of the fairly steep frequency-response slope characteristic of the Starr table, the respiratory frequency is relatively attenuated to such a degree that the subject's breathing does not

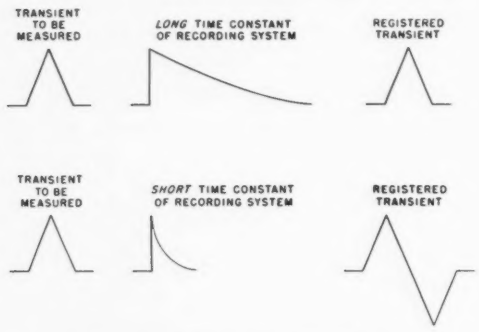

FIG. 3. Differentiation effects which are introduced to distort a wave when the time constant of the recording system is too short.

make the ballistocardiogram unreadable as is true when a system with a flat frequency response is used.

When a ballistocardiograph has a rising frequency response characteristic in the working frequency spectrum, it may be considered as having a time constant. The steeper the slope of the curve, the shorter is the effective time constant. When the time constant is short as compared with the frequency of the ballistic waves, a form of distortion is introduced known as differentiation. To illustrate, let us assume that we have a triangular wave (fig. 3) which is to be registered. If the time constant of the recording system is long as compared with the transient wave to be measured, the triangle will register faithfully. If the time constant is short, the triangle will register as shown with a negative wave which is symmetrical but negative. In ballistocardiography this manifests itself in a form of distortion where positive waves such as the J will be followed by a deep K wave even though no K wave is present in the subject. If the time constant is somewhat longer but still too short for accurate registration of the transient wave, a partial differentiation will take place and register the negative wave but with a lesser negative magnitude. The presence of K waves in ballistocardiograms registered with undamped tables when they should not be present as in coarctation of the aorta is explainable by the differentiation principle. Deep negative waves are likewise differentiated which produce positive after waves such as an L after a deep K wave.

Another severe form of distortion, technically known as phase shift, may occur in ballistocardiograms. Phase shift is the lag of deflection behind the applied force. Figure 4 shows the angle by which the deflection lags behind the applied ballistic force for different values of underdamping and for varying frequencies relative to the resonant frequency of the ballistocardiograph.* In reading lag in degrees from figure 4 it should be kept in mind that there are 360 degrees to a complete cycle. Thus a 90 degree lag as read from the graph is equivalent to a delayed displacement or a temporal lag of one-fourth of a cycle; 45 degrees corresponds to a lag of one-eighth of a cycle. When simultaneous physiologic events are registered with relation to the ballistocardiogram and phase displacement is present in the ballistocardiogram, error in interpretation with regard to the temporal inter-relationships of the component waves will result. It is obvious from figure 4 that the better the damping and the higher the natural frequency, as compared with the component frequencies present in the ballistic movements of the body, the less will be the phase displacement.

To illustrate the magnitude of phase dis-

* The curves of figure 4 are representative of vibrating systems[18, 19] and are known to students of vibration mechanics. The ballistocardiograph table is a vibrating mechanism which falls into this classification and should perform precisely as indicated by the curves.

placement in a Starr table, let us consider one with a natural frequency of 9 cycles per second when loaded with a mass equivalent to a subject and let us assume that the system is 50 per cent damped; Starr has suggested that this is an approximate value for his 9 cycle table. A 2 cycle per second wave will show a phase lag of about 14 degrees; a 4 cycle per second wave about 30 degrees; a 6 cycle per second wave about 50 degrees; an 8 cycle per second wave about 77 degrees; a 10 cycle per second wave about 103 degrees.

When a subject is placed upon a Starr table, it is next to impossible to clamp the skeletal structure to the table so that there is no relative movement possible. This is especially true because we are dealing with minute ballistic body movements; if large body movements were normal, this effect would be negligible. Thus, it is obvious that we are dealing with an over-all vibrating system of multiple component vibrations successively coupled to one another in a very complex manner. The major component vibrating systems are the heart, the body and the table. The vector sum of all the vibrating components of the subject when added to the characteristics of the table produce the resultant ballistocardiogram.

Some years after Starr devised his ballistocardiographic table, Nickerson[2] developed a critically damped table which had a natural frequency of approximately 1.5 cycles per second when loaded with a subject of average weight. The reason Nickerson employs such a table is that he believes from certain assumptions that such a table would move in unison with the body and register a truer record of the ballistic motions of the body for the primary frequencies than is possible with the Starr table. Hamilton and his co-workers,[6] in conclusion to their experimental observations, do not agree with Nickerson.

Basically, the Nickerson table is similar to the Starr table with the exception of the stiffness of the suspension springs. Nickerson uses much softer springs so that the subject-loaded table drops to a natural frequency of 1.5 cycles per second. Nickerson obtains critical damping by means of an ingenious oil system which is adjustable for critical damping for each subject. By varying the opening of a valve in the oil system, the damping of the table may be varied from an underdamped to an overdamped condition. To test for the degree of damping, the operator merely deflects the table and then releases it. A kymographic registration of the table movement indicates whether critical damping is obtained. In figure 5 are representative schematic kymographic records of underdamped, critically damped and overdamped tables.

In figure 6 may be seen the frequency response curve of a critically damped Nickerson

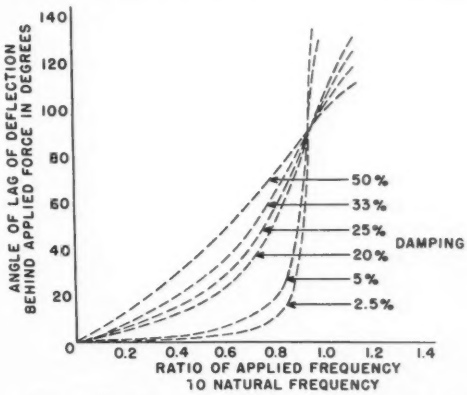

FIG. 4. Family of curves which are characteristic of vibrating systems. The ballistocardiograph which is such a vibrating system may be represented by these curves and the amount of lag of deflection behind the applied ballistic force may be evaluated if the degree of damping is known.

table when loaded with a weight equal to that of a human subject.* Note that from zero cycles per second and above there is a gradual diminution in the response of the ballistocardiograph with respect to frequency. For example at 1 cycle per second the response is down to 70 per cent of normal; at 1.5 cycles per second, which is the natural frequency, the response is down to 50 per cent; at 3 cycles per second the response is down to 19 per cent; and at 4 cycles per second the response is only 10 per cent. Above 4 cycles per second the

* This is a curve which may be a member of the family of curves of figure 2 and represents the special condition when critical damping is present.

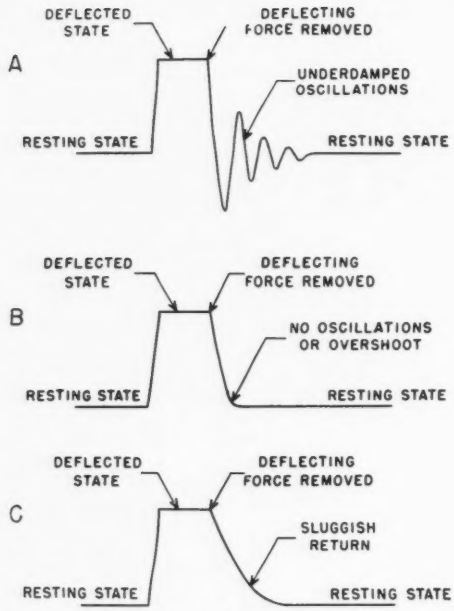

FIG. 5. Illustrations of kymographic registrations with a Nickerson ballistocardiograph to illustrate: *A*—underdamping; *B*—critical damping; *C*—overdamping.

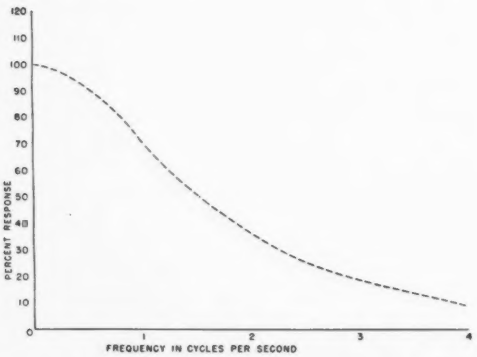

FIG. 6. Frequency response curve of a critically damped vibrating system whose natural frequency is 1.5 cycles per second. This curve is derived from the family of curves of figure 2 and satisfies the condition for critical damping. The critically damped Nickerson ballistocardiograph is such a vibrating system and its response with respect to frequency may thus be evaluated.

response of the instrument is nil. It has been shown that a ballistocardiograph must be capable of registering at least up to 6 cycles per second and preferably to 10 cycles per second to obtain an accurate configuration in the ballistocardiogram. Such a ballistocardiograph would have to have a frequency response curve that is flat at 100 per cent response from zero to about 10 cycles per second. If the Nickerson type table is employed with an adjustable damping mechanism, then a critically damped table with at least a natural frequency of 30 cycles per second would approximately satisfy the condition as indicated in figure 7. Note that at 10 cycles per second the response is 90 per cent of normal. It should also be noted that critically damped ballistocardiograph tables are always down to 50 per

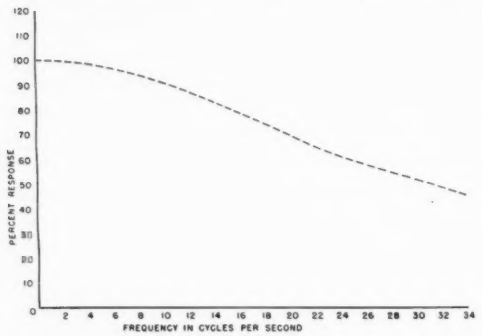

FIG. 7. Frequency response curve of a critically damped table but with a natural frequency of 30 cycles per second instead of the usual 1.5 cycles per second. This curve is derived from figure 2 and satisfies the condition when critical damping is present.

cent response at natural frequency and that all response curves droop as the frequency is increased. Actually, if a very close approximation to flat response up to 10 cycles per second is to be procured, the natural frequency would have to be considerably above 30 cycles per second.

Due to the fact that the frequency response curve of a Nickerson type table does not have a rising characteristic with frequency as does the Starr table, the former does not possess a shortened time constant. As a result, ballistic waves are not differentiated and this form of distortion is not present. However, the drooping characteristic of the 1.5-cycle natural frequency table introduces another form of distortion similar to phase displacement. Let us

consider a condition where a triangular impulse is applied to the Nickerson table. In figure 8 the abscissa is plotted in terms of time divided by the natural period of the table; deflection time is equal to half the undamped natural period. Deflection time is the time consumed by the table to traverse a deflection when an instantaneous impulse is applied. If for example the applied triangular impulse has a base which is equal to twice the natural period of the table, the response of the critically damped ballistocardiograph will be shown. It may be seen that the registered impulse is increased in width by about 10 per cent and decreased in amplitude by about 17 per cent. For impulses of longer duration, the loss in amplitude is less because loss in amplitude is inversely proportional to the width of the baseline. It may also be noted that the recorded impulse has shifted by about 25 per cent of the natural period which is the phase shift. Obviously, as the deflection time or natural frequency of the table is increased, errors due to phase shift are reduced.

Because of the drooping frequency response characteristic of the Nickerson table which falls in the working frequency spectrum of ballistocardiography, three forms of distortion are introduced, namely, reduced amplitudes of complexes, increased duration of complexes and phase displacement. Serious complications in interpretation of the ballistocardiographic complexes with respect to other simultaneously registered physiologic events may therefore be introduced.

As a result of the excellent low frequency response of the Nickerson table, respiratory weaving will be superimposed upon the ballistocardiogram in many cases with an amplitude sufficiently large to throw the kymograph recording mechanism beyond the limits of the graph. As a result, breathing must be suspended while the ballistocardiogram is being taken. In many applications the cooperation of the subject cannot be obtained and effects or variations in the ballistocardiogram cannot be evaluated during the respiratory cycle. Also, variations due to Valsalva or Mueller effects cannot always be completely avoided when the subject is required to suspend breathing.

The fact that ballistocardiographic waves may be registered directly from the body (without the use of a suspended table) while the subject is in a supine position had been observed by Nickerson[2] and Hamilton and co-workers.[6] They registered the relative movements of the vertex of the head and a rigid table or support upon which the subject was allowed to rest. Dock and Taubman[3] duplicated the procedure. Although the recorded waves appeared to be of a fair quality, head tremors, and kyphosis caused bizarre ballistocardiograms. Dock and Taubman[3] then suggested a photoelectric and an electromagnetic method for registering relative movement between the shins and the rigid supporting table. They observed that the shins were

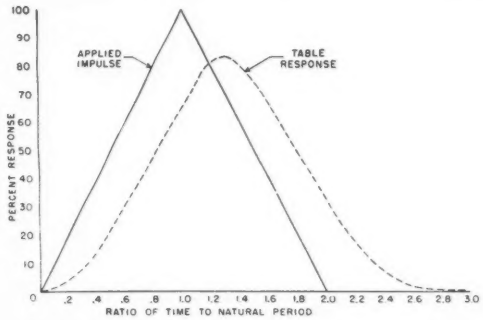

FIG. 8. Calculated response of a critically damped Nickerson ballistocardiograph to a triangular ballistic impulse.

more desirable as a source of ballistic movement reference because of reduced orthopneic tremor. The photoelectric method was claimed to register a displacement ballistocardiogram whereas the electromagnetic unit registered the velocity characteristic of ballistic movement. The comparatively simple technic of Dock and Taubman and the subsequent popularization of the method by Dock, has done much to stimulate interest in clinical ballistocardiography. Later, Sheehan and associates[13, 14] described a piezoelectric ballistocardiograph in which barium titanate was the detecting element.

When a subject is allowed to rest in a supine position on a hard surfaced rigid table, he will possess a natural frequency and a degree of

damping which is dependent upon tissue compliance and the subject's weight; the head support and the heel support exhibit modifying effects although the latter is the more marked. Dock suggests a small pillow under the head and a wooden block under the ankles so that the heel of the foot does not rest on the table. All of the data previously discussed in this report which applies to vibrating systems, such as natural frequency, damping, phase displacement, and amplitude attenuation, applies to a subject when placed on a hard-surfaced rigid table. Furthermore, when the subject is placed on a Starr or Nickerson table, it is not possible to prevent the subject from exhibiting these vibrating properties with respect to the table for the small motions involved no matter how the body is supported or clamped. Therefore, it would seem that the use of a suspended table merely introduces variables or distortions in the ballistocardiogram which would not be present if the ballistic movements were registered without the use of a table. Furthermore, the use of a comparatively simple ballistocardiograph which does not require a suspended table does seem extremely enticing and applicable to routine clinical procedures.

Unfortunately, however, this procedure of registering ballistocardiograms is not free of error. In the first place, the natural frequency of the body falls in the spectral region of the ballistic frequency components. Therefore, the frequency response as a function of the ratio of the applied frequency to natural frequency for different degrees of damping is not flat. The degree of damping is not the same for all persons which additionally complicates the situation. With optimal technic, considerably less than 50 per cent damping is obtainable on the average subject which introduces differentiation effects and phase distortion. The type of foot support definitely affects the magnitude, damping and the temporal positioning of the component waves in the ballistocardiogram. An inflated plastic cushion, a feather pillow, wooden block and a sand bag as a foot support will affect the natural frequency and damping of the body differently. The higher the natural frequency, the more accurate will be the registered ballistocardiogram. A sand bag, as suggested by Herzman,[15] when placed under the ankles appears to produce the best condition. Due to the high degree of compliance of the joints leading to the head, the support under the head produces a lesser effect upon over-all damping and natural frequency. A padded table lowers the effective natural frequency markedly and reduces the degree of damping. Therefore, the best one can do is use the technic which will produce the highest natural frequency and maximum damping. In figure 9 may be seen the effects of technic upon damping and natural frequency.

Instrumental characteristics which are unsuitable for ballistocardiography can introduce distortion of a magnitude much greater than one must put up with in the subject. Fortunately, instrumental characteristics are completely controllable but inadequate consideration has been given to this phase of the subject. Many forms of ballistocardiograph which do not employ the suspended table are in use and an analysis of their characteristics is in order.

Let us first consider the ballistocardiograph originally suggested by Dock and Taubman.[3] Basically, their apparatus consisted of a coil of fine wire which was placed in a magnetic field. Relative movement between the coil and the magnet was accomplished by supporting the coil on a hinged mechanism which was activated by a cross bar located on the subject's shins. The rest of the mechanism was placed on the table between the subject's legs. The coil was connected to an electrocardiograph and the potentials generated in the coil as a result of ballistic movements was registered.

The magnitude of the voltage generated in the coil may be expressed by the formula

$$e = N\frac{d\phi}{dt} \text{ abvolts} = 10^{-8}N\frac{d\phi}{dt} \text{ volts} \qquad (1)$$

where e = voltage generated in the coil as a result of ballistic movement
N = number of turns of wire in the coil
ϕ = flux linkages or magnetic lines of force which surround the coil
t = time

According to formula 1, the voltage which is

induced in the coil as a result of relative movement with respect to the fixed magnetic field is equal to the product of the number of

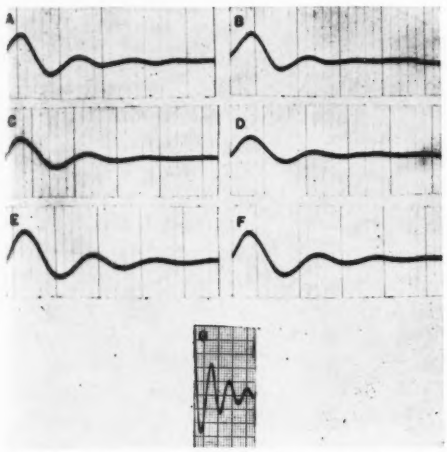

FIG. 9. The effects of technic upon natural frequency and damping. Records *A* through *F* were taken on a 135 pound male 5 feet 8 inches tall. The sensitivity of the recorder was lowered so that ballistocardiograms would not register. The subject was deflected along the long axis (head-foot) and suddenly released. Record *A* was taken with a plastic pillow under the head and a sand bag under the ankles. The natural frequency is approximately 4.10 cycles per second. The ratio between adjacent positive and negative lobes is 1.7 to 1 which represents marked underdamping. A 5 to 1 ratio would represent 50 per cent damping; the higher the ratio the better is the damping. Record *B* was registered with the pillow removed, the natural frequency is unchanged but the lobe ratio is 3.2 to 1. Record *C* was taken with a plastic pillow under the head and a wooden block under the ankles. The natural frequency is 3.35 cycles per second and the lobe ratio is 1.7 to 1; with pillow removed (*D*) the natural frequency is unchanged and the lobe ratio is 2.2 to 1. Record *E* was taken with plastic pillows under the head and ankles. The natural frequency is 3.13 cycles per second and the lobe ratio is 2.2 to 1; with head pillow removed (*F*) the natural frequency is unchanged and the lobe ratio is 2.1 to 1. Record *G* was registered on another subject with a pillow under the head; heels were allowed to extend beyond the bounds of the table. The natural frequency is 3.85 cycles per second and the lobe ratio is 1.1 to 1.

turns in the coil by the rate at which the lines of force are cut. It may be seen that if a ballistic wave has a higher frequency, the rate at which the lines of force are cut is increased, and, therefore, the voltage is higher even though the magnitude of relative movements is constant. The response curve (pure velocity) of such an instrument possesses a rising characteristic with respect to frequency as shown in figure 10.

From the material previously discussed, it should be apparent that the original Dock-Taubman instrument shows the following effects:

1. It does not register all of the component ballistic frequencies with amplitudes which are independent of frequency.
2. The instrument measures velocity rather than displacement. Actually, when the subject's response is vectorially added to

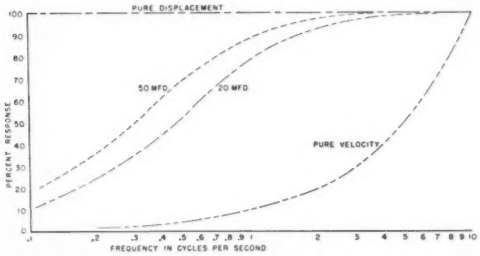

FIG. 10. Curves which show the frequency response relationships between displacement and velocity. In addition, the calculated response of the Dock magnetic ballistocardiograph which is equalized by 50 microfarad and 20 microfarad condensers is shown.

that of the instrument response, the over-all response is no longer a pure velocity curve.
3. Marked differentiation is introduced in the ballistocardiogram.
4. Marked phase displacement is present.
5. No limitation to high frequency response is present.
6. No weave is superimposed upon the ballistocardiogram due to respiration.
7. The configuration of the ballistocardiogram resembles one obtained on the same subject with a Starr table.

The original design of the Dock-Taubman ballistocardiograph had a rather serious mechanical defect. The hinged mechanism had sufficient friction to effect the true movement of the hinge with the result that some of the registered waves appeared truncated. The

modified design of the Dock magnetic ballistocardiograph[16] overcomes this defect by the elimination of the hinge. In addition, the modified instrument introduces what is electrically known as equilization by the addition of a 50 microfarad condenser across the coil. Equilization modifies the slope of the frequency response curve to make it approach the response of a displacement type ballistocardiograph (fig. 10); a displacement ballistocardiograph has a flat frequency-response curve. Equalization accomplished with 50 microfarad and 20 microfarad condensers shunting the coil in the Dock magnetic ballistocardiograph is shown. It may be seen that when 50 microfarads are used, the frequency-response curve begins to approach the pure displacement curve from 1 cycle per second to the upper limits of the frequency component waves that may be found in ballistic impulses. From figure 10, it may also be seen that the larger the condenser, the closer will be the approach to pure displacement type registration. The more important characteristics of the most recent version of the Dock ballistocardiograph are

1. It possesses a fair approximation to a displacement characteristic for ballistic frequencies.
2. The larger the capacity of the shunting condenser, the better is the approximation to true displacement type registration.
3. The larger the capacity of the shunting condenser, the less is the attenuation effect upon respiration frequencies. As a result, the more will be the respiratory weave which will superimpose itself upon the ballistocardiograph.
4. Phase displacement which is introduced by the instrument diminishes as the shunting capacity is increased. There is some phase displacement present when a 50 microfarad condenser is used but not of sufficient magnitude to be serious.
5. Distortion due to differentiation is present but small when a 50 microfarad condenser is used.
6. The ability of the instrument to register higher ballistic frequencies is not impaired by equalization.
7. The configuration of the registered ballistocardiogram will not be similar to one taken on the Starr table or the original unequalized Dock-Taubman apparatus.

Dock and Taubman also described a photoelectric ballistocardiograph which was used on the shins. The essential difference between the original electromagnetic ballistocardiograph and the photoelectric apparatus is the substitution of a photoelectric cell and light bulb with an occluding vane for the coil and magnet. The vane was attached to the hinge and ballistic body movements varied the amount of light falling on the cell which modulated the photoelectric cell. The cell was in turn connected to the electrocardiograph with a condenser located in one of the two connecting wires. The authors called their photoelectric method a displacement type ballistocardiograph. Although a photoelectric system such as used by Dock and Taubman is a displacement system, the addition of the series condenser for the purpose of eliminating respiratory weave introduced a rising frequency-response characteristic in the ballistic frequency spectrum. As a result, the instrument did not register displacement ballistocardiograms with the resultant forms of distortion inherent in such a system.

The piezoelectric or barium titanate crystal described by Sheehan and associates[13, 14] when used as a sensing element in ballistocardiography possesses rather interesting properties. The more commonly used piezoelectric crystal made of rochelle salt is more sensitive than barium titanate but it is not as stable as a function of temperature, and it is permanently damaged if exposed to temperatures above 115 F., or if located for prolonged periods in excessively low or high humidities.

Piezoelectric crystals possess the property of generating electrical voltages when squeezed or twisted, and the magnitude of the voltage is proportional to the applied force. The electrical potentials are led off from the crystal by means of metal foil electrodes which are cemented to the opposite faces of the crystal. The combination of crystal and electrodes with zero pressure or twist applied may be considered a condenser with a finite capacity When physical pressure or twist is applied

the crystal acts like a generator with a condenser in series with it. The electrical energy which is developed in a piezoelectric crystal is extremely small although the voltage generated may be of fair magnitude.

When a piezoelectric crystal is used for ballistocardiographic purposes, it is cemented to a cantilever which is flexed. A cross bar is placed on the shins and the movement of the cross bar deflects the cantilever, one end of which is rigidly fastened to the table. In turn, the piezoelectric crystal is flexed and a voltage which is proportionate to movement is generated across the crystal electrodes. This voltage is applied to an amplifier type electrocardiograph and registered as one would an electrocardiographic lead. A string machine cannot be used because the energy generated by the crystal is too small to deflect the string. If an amplifier is interposed between crystal and string, the combination will function.

The electrical loading which the amplifier presents to the crystal may be considered as resistive and the voltage which is delivered to the amplifier is equal to the voltage generated by the crystal minus the voltage drop across the effective capacity of the crystal. The distortion which may be introduced by the effective capacity of the crystal is dependent upon the rate at which the voltage which is generated by the crystal varies and upon the relative values of the crystal capacity and the amplifier input resistance. The product of the crystal capacity and the input resistance of the amplifier is the time constant in seconds if the capacity is expressed in microfarads and the resistance in megohms.

In order for the ballistic voltages to be applied to the amplifier with a configuration nearly equal to the voltages generated by the crystal, it is necessary that the time constant be of the order of at least a second. Otherwise, errors due to differentiation effects, relative amplitude distortion of the component frequencies and phase displacement will be present. The capacity of a usual crystal element is equal to approximately several thousandths of a microfarad. In order to attain a time constant of about 1 second or more, the resistance in the circuit would have to approach impractical values. The piezoelectric ballistocardiographs described in the literature possess time constants which introduce the distortions described.

A piezoelectric ballistocardiograph may be designed with an adequate time constant and still retain a reasonable value of resistance by shunting the crystal with a large condenser.[17] The resultant sensitivity is very markedly reduced but by proper design it may be possible to attain adequate voltages from such a system.

Another source of trouble with the piezoelectric method is the necessity for making direct contact between table and subject via the instrument. If the compliance of the instrument is not high, the ballistocardiogram may be distorted. We have observed that even a moderately high degree of compliance may introduce distortion in the ballistocardiogram. Most of the distortion is probably due to the shifting of the tissue over the tibia when a retarding force is present.

For our studies we devised a photoelectric type ballistocardiograph* which differed from the Dock-Taubman arrangement. Instead of a cross bar, we used a considerably heavier apparatus across the shins. Our cross bar has built into it an optical system which allows a rectangular field of light to be thrown upon half the photo sensitive portion of a barrier layer photoelectric cell. The photoelectric cell is allowed to rest on the table and the relative movement of the field of light and the cell varies the amount of light which falls upon the photosensitive element of the cell. The voltage which is generated by the cell is proportional to the amount of light which strikes the photosensitive element thereby making the system a pure displacement ballistocardiograph. The output of the cell is connected to an amplifier type electrocardiograph. The only physical connection between the cross bar and the stationary cell is a beam of light which does not introduce compliance effects nor the difficulties with the Dock-Taubman hinge.

Another important difference between our photoelectric ballistocardiograph and the Dock-

* Manufactured by Sanborn Company, Cambridge, Mass.

Taubman arrangement is in the filter system. The latter introduced a condenser in series with the photoelectric cell and the electrocardiograph to eliminate respiration weave of the ballistocardiographic base line. When a condenser is introduced which adequately attenuates the respiratory weave, the time constant is shortened sufficiently to introduce the errors previously discussed. Our instrument circumvents the time constant effects by allowing the operator directly to couple the photoelectric cell to the electrocardiograph by means of a toggle switch. In one position of the switch, the pure displacement response of figure 10 is attained and the subject must suspend breathing when ballistocardiograms are registered. Error due to differentiation, frequency-amplitude attenuation and phase displacement are not present in the instrument although it cannot be eliminated in the subject because of the low natural frequency and underdamping which must be contended with. The most precise ballistocardiogram is obtained if Valsalva and Mueller effects are minimized and if the best possible technic is used which produces the maximal natural frequency and damping of the subject with pure displacement registration.

Suspended respiration is not always practical in clinical ballistocardiography and a means for minimizing distortion consistent with optimal attenuation of the respiratory frequencies is a necessity. In order to accomplish this, we devised a resistance-capacitance type parallel-T network attenuator which is interposed between the photoelectric cell and the electrocardiograph by throwing the toggle switch in the opposite direction. This type of attenuator when designed to produce maximum attenuation at 0.3 cycle per second, which corresponds to a respiratory rate of 20 per minute, produces a much flatter frequency response curve than is possible with a series condenser except in the respiratory-frequency spectrum. The curve will fall between the 50 microfarad and the 20 microfarad curves of figure 10 in the ballistic frequency spectrum (1 cycle per second and above) and attenuate the respiratory frequencies (1 cycle per second and below) to a greater degree. Our experiences have shown that although such a response does not completely eliminate distortion, it makes possible the registration of a clinically usable ballistocardiogram in the presence of respiration.

We have also observed that either a very light cross bar or a moderately heavy one gives best results. A moderately heavy cross bar reduces the relative movement between tibia and cross bar during ballistic body movements. The maximal weight that may be used is consistent with subject comfort only. The very light cross bar will apparently also ride on the shin without relative movement with the tibia. Considerable distortion may be introduced if the heavy cross bar is allowed to rest on muscle.

Amplifier type electrocardiographs are resistance-capacity coupled and thereby possess a time constant of at least 2 seconds or equivalent. The frequency response curve is good down to 1 cycle per second. The droop in response below 1 cycle per second is too gradual to attenuate effectively the respiratory frequencies. Such a frequency-response characteristic does not distort the ballistocardiogram.

An experiment was performed to illustrate the effects of phase shift, amplitude distortion and differentiation for varying time constants. A typical ballistocardiogram was generated by means of a rotating disc whose circumference was cut out in polar coordinates. The rotating disc in turn modulated light which fell on the photosensitive surface of a photoelectric cell through an appropriate optical system. The output from the photoelectric cell was allowed to pass through electrical circuits of differing time constant and were simultaneously registered on a four-channel recorder. The resultant record is shown in figure 11. The "control" would be equivalent to a pure displacement ballistocardiogram as registered with a photoelectric ballistocardiograph and no condenser or filter interposed between the cell and the recorder or electrocardiographic apparatus. The paper speed was 50 mm. per second and each time line increment represents 0.02 second. The record with an 0.025 second time constant represents velocity recording, and the 0.1 second recording is an approximation

of a commercially available piezoelectric ballistocardiograph. Note the effects upon amplitude, differentiation effects and temporal relationships. The effect of underdamping and low natural frequency of the human body would further modify the ballistocardiogram. Figure 11 merely illustrates the form of distortion which an improperly designed Dock type of instrument will introduce.

The customary procedure which has been used to date in calibrating a Starr or a Nickerson ballistocardiograph is to apply a longitudinal force to the table (head-foot direction) and observe or register the magnitude of deflection. The longitudinal force is produced by means of a suspended weight; a pulley is used to change the gravitational pull on the known weight to a longitudinal pull. The recording mechanism which registers the table movement may be in the form of a Hamilton manometer, a strain gauge or capacitance transducer, or any other sensing element which is capable of registering table movement down to zero cycles per second which represents a constantly applied force. The amplitudes of the registered ballistocardiographic waves are then evaluated on the basis that if a force of X grams produces a deflection of Y millimeters in standardization, a ballistic wave may then be evaluated.

This calibration procedure is *known as static calibration and may lead to gross error in evaluating the ballistocardiogram.* We have shown that the frequency response curves of both the Starr and the Nickerson ballistocardiographs are not flat. That is, as the applied force varies its frequency, the response of the ballistocardiograph changes. The ballistocardiogram is composed of waves of differing frequency and they will register with different amplitudes even though the magnitude of the applied force may be unaltered. Unless the over-all frequency response of the ballistocardiograph is known and the frequency components of each ballistic wave are determined, the static calibration relationship to the ballistic force in the head-foot direction cannot be inter-related. In addition, a further complication is introduced when a live subject is placed on the ballistocardiographic table. We have shown that it is impossible to clamp the skeletal structure to the table so that no relative movement is possible. We have also shown that a subject in the usual position possesses a frequency response which is not

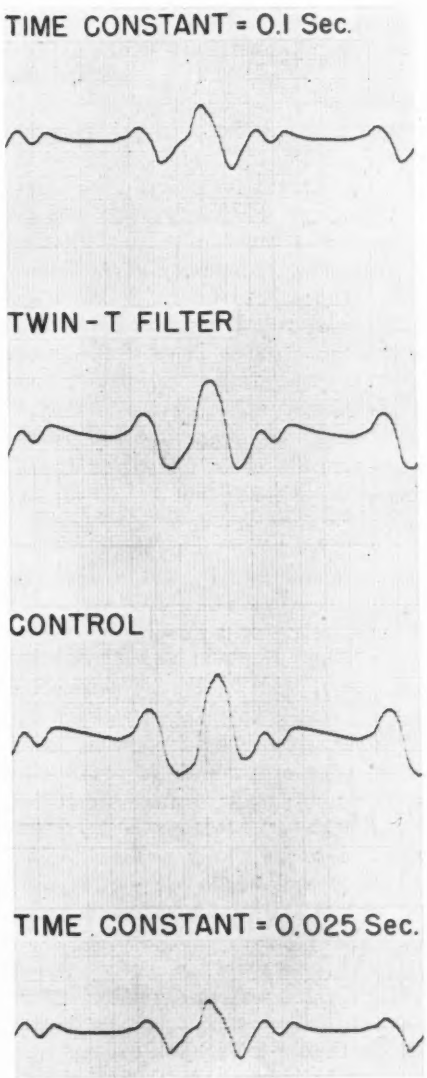

FIG. 11. Simultaneously registered ballistocardiograms to illustrate the effects of phase shift, amplitude distortion and differentiation for varying time constants. The indicated time constants may be found in ballistocardiographs presently in use.

flat with respect to frequency and that there is considerable variation from one person to another. The over-all frequency response curve of the table must be added vectorially to that of the subject and the resultant evaluated. This is definitely not a clinically feasible procedure

The true calibration must be obtained under dynamic conditions and there is no known simple procedure for doing this. Starr has tried dynamic calibration (described in his first paper on ballistocardiography) where he imposed impacts simulating the ballistocardiogram into the heads of cadavers lying on a table and these impacts were delivered at increasing rates. The trouble with this procedure is that a great deal of calculation must be introduced before a very rough approximation is obtainable with respect to the overall response on each subject. This again is not a practical clinical procedure!

Let us assume that a simple dynamic calibration procedure were possible. Further modifications due to the spatial force vector projections along the head-foot axis and compliance effects would be present. It is our opinion that calibration procedures with regard to amplitude in the ballistocardiogram from a clinical standpoint should be treated with extreme caution.

Ballistocardiograms which are registered from the shins may be statically calibrated even though the systems are completely insensitive to constantly applied deflections. A simple procedure is to push on the subject's head with a scale calibrated in grams at a slowly changing rate. The maximal push in grams and the amount of deflection registered is the calibration. Here again the frequency response of the instrument must be vectorially added to that of the subject, and the over-all treatment is identical to that of the table method. Obviously, the accuracy is no better nor worse than the static calibration procedure with the suspended table and is just as involved.

About all that is justifiable from a calibration standpoint with both the table and shin ballistocardiographs is to maintain over-all instrumental sensitivity at a known or constant value for the observation of gross ballistic changes only. An instrument such as we have used satisfies this condition because the light intensity is fixed, the photoelectric cell is inherently of constant sensitivity and the electrocardiographic recorder sensitivity is adjustable to a predetermined value. If further check on sensitivity is desired, the calibration procedure which we have described may be used. However, the reading of amplitude relationships other than gross changes *must* be done with extreme caution on all of the ballistocardiographic systems we have discussed.

Conclusions

1. The ballistic force vector which imparts the movement to the body is of variable magnitude throughout the cardiac cycle and its spatial direction changes.

2. The amount of movement which is imparted to the body by the spatial force vector of cardiac origin is dependent upon factors such as the compliance of the tissues between the heart and the skeletal structure, the compliance of tissues between the vascular system and the skeletal structure, the compliance of the various skeletal joints, the mode of support of the body, the compliance of the tissue between the skeletal structure and the support, and the elasticity and peripheral resistances of the vascular system.

3. The ballistocardiograph, in its common form is capable of measuring ballistic body movements along the long axis of the body only. Ballistic forces that exist in the body are spatial, therefore, the projection of the instantaneous spatial vector along the long axis of the body is measured. The projected instantaneous vector is of a lesser magnitude than the spatial vector and the body moves a lesser amount along the long axis than in the direction of the instantaneous spatial vector. Unless the ballistic body movements are known in three dimensions, quantitative estimations of cardiac output are unwarranted.

4. Modifications to body movement which are introduced by anatomic compliances (item 2) hinder the exact evaluation of cardiac output from the ballistocardiogram. Thus, only gross

changes in cardiac output in the same person may be crudely estimated.

5. There are three basic types of ballistocardiograph presently in use, namely, the so-called high frequency undamped Starr table, the low frequency critically damped Nickerson table, and the method popularized by Dock which does not require a suspended table.

6. The Starr table introduces several forms of distortion, namely, amplitude distortion with respect to frequency, phase displacement, and differentiation effects.

7. The Nickerson table does not introduce differentiation but is incapable of registering the higher frequency components, exhibits phase and duration distortion and amplitude distortion with respect to frequency.

8. The original Dock-Taubman ballistocardiographs introduced amplitude distortion with respect to frequency, phase displacement and differentiation effects. The more recent Dock electromagnetic type with equilization has some of these distortions present but of a lesser amount.

9. The photoelectric ballistocardiograph of our design permits the selection of pure displacement or distortionless response or, with the introduction of a parallel-T network attenuator, an amount of distortion approximately equal to that registered with the more recent Dock equalized-electromagnetic ballistocardiograph. However, the parallel-T network attenuates the respiratory weave more efficiently.

10. When a subject is allowed to rest in a supine position on a hard-surfaced, rigid table, he will possess a natural frequency and a degree of damping which is dependent upon the tissue compliance, weight and the mode of support of the heels and head. The natural frequency falls in the frequency spectrum encountered in ballistocardiography which introduces distortion which cannot be eliminated. Furthermore, the degree of damping is variable and the subject is well underdamped which contributes to the magnitude of distortion.

11. When a subject is placed on a Starr or Nickerson table, it is impossible to prevent the subject from exhibiting a natural period of vibration independent of the table no matter how well the body is supported or clamped for the minute ballistic movements. Therefore, the response characteristics of the body must be vectorially added to the characteristics of the table. In such case, table distortions are introduced.

12. Extreme caution must be taken to keep the compliance high when the cross bar across the subject's shins is mechanically coupled to a stationary object. Too low a compliance may introduce a slight relative movement between tibia and cross bar which will distort the ballistocardiogram.

13. There is no known way of attenuating respiration weave without slightly distorting the ballistocardiogram. The parallel-T network attenuator allows a close approach only. Suspended respiration is not always practical. Therefore, with the present knowledge of the art, we believe that both methods should be made available to the operator and the distortions which may result taken into consideration.

14. In evaluating ballistocardiograms, especially when simultaneously registered with other physiologic events or when measuring the duration of ballistic complexes, the degree of subject damping and the natural frequency should be determined. With these data available, reference may be made to the graphs discussed in this paper and the approximate amount of temporal displacement of the registered ballistic complexes may be estimated and the necessary correction factor may thus be made.

15. Ballistic body movement may be measured in terms of magnitude (displacement), body speed (velocity) and the acceleration which the body experiences in attaining the speed of traversal. Mathematically, body motion may be represented as a vector quantity which possesses magnitude and direction; velocity is the derivative of displacement, and acceleration is the derivative of velocity. Each of the three forms of measurement supplies distinct and pertinent information which must be properly evaluated and interpreted. Instruments which markedly modify the intended characteristic so that the performance is neither true displacement, velocity or ac-

celeration will confuse ballistocardiographic interpretation.

16. Suspended table type ballistocardiographs such as the Starr and the Nickerson are generally calibrated by applying a constant force in the head-foot direction. This is known as static calibration. Due to the fact that neither the Starr or Nickerson ballistocardiographs have equal sensitivity of deflection throughout the frequency spectrum encountered in ballistocardiography, static calibration is quite meaningless for the estimation of the ballistic force which is responsible for the production of a ballistocardiographic wave.

17. A further complication in the use of static calibration is that it does not take into consideration the relative movements of the patient with respect to the suspended bed. The response characteristics of the subject must be vectorially added to the characteristics of the bed.

18. A calibration method is described for shin type ballistocardiographs but its accuracy is limited by the same factors which affect the table type ballistocardiograph.

19. Dynamic ballistocardiographic calibration is necessary for the evaluation of the ballistic forces of cardiac action. Unfortunately there is no simple clinical method known. Until such a method is developed, it is not dvisable to make quantitative amplitude measuarements in ballistocardiography.

20. The physical analysis presented definitely indicates that there are inherent distortions present in ballistocardiography. When making physiologic and clinical application, it is most important to keep in mind the limitations of the method. To date, it is our belief that the art has been hindered by the many fantastic claims made in the literature without due consideration to the inter-relationships of the physical and physiologic principles involved.

Sumario Español

Un analisis físico se presenta del método de Starr, Nickerson y Dock de registrar el balistocardiograma. Se demuestra que muchas formas de distorción están presentes. Alguna de la distorción puede estar presente debido a la instrumentación que puede ser controlada, y otras formas de distorción son inherentes al sujeto que se esta examinando, estas últimas son mas difíciles de controlar y evaluar. El efecto que algunos de los variables no controlables tienen en la amplitud y posición temporera de las ondas balistocardiográficas se analizan. El estado de la normalización estática y dinámica de los procedimientos se discute. Un glosario de las voces técnicas se incluye.

Glossary* of Technical Terms

Acceleration ballistocardiogram: a graphic registration of the acceleration which the body experiences. The temporal relationships of the component waves are different than in a velocity or a displacement ballistocardiogram.

Attenuation: the process of lessening or diminishing the amount of force or stimulation or the recorded effects.

Axially: when used in ballistocardiography, the head-foot direction along the body.

Cantilever: a projecting beam which is supported only at one end.

Compliance: the physical yielding characteristic of matter when a force is applied to it. The compliance of matter is generally expressed in centimeters per dyne.

Condenser: an electrical device which is used in electrical circuits for holding or storing an electrical charge.

Critical damping: (See damping.) when a certain predetermined amount of friction is introduced in an object such as a ballistocardiographic table and a force is instantaneously applied to the table, the table will deflect with a dead beat; it will neither overshoot nor consume excessive time in reaching its destination.

Damping: the introduction of friction in a mechanical system and resistance in an electrical system.

Deflection time: the time consumed by an object such as a ballistocardiograph table to traverse a deflection when a constant force is suddenly applied.

Displacement ballistocardiogram: a graphic registration of the magnitude of body movement which results from cardiac action recorded with respect to time.

Dyne: a unit of force in the metric system of physical units. It is such a force that under its influence an object whose mass is 1 Gm. would experience during each second an increase in velocity of 1 cm. per second.

* This has been introduced at the request of the Editor who was of the opinion that some of the definitions would be helpful to some readers who are not familiar with the field of vibration mechanics and some of the other fields referred to in this paper.

EQUALIZATION: an electrical procedure for modifying the effective frequency response of a system in order to compensate for the inherent deficiency of one or more components of the system.

FREQUENCY RESPONSE CURVE: a performance graph of a vibrating system such as a ballistocardiograph table in which the axis of abscissas is expressed in cycles per second and the axis of ordinates represents the corresponding response of the table to an applied force of constant magnitude at different frequencies. A flat frequency response occurs when the vibratory response of the system does not change with the frequency of the applied force.

FREQUENCY SPECTRUM: the distribution of vibrating energy with respect to frequency.

HARMONIC: a component vibration of a complex wave which is an integral multiple of the fundamental frequency of the complex wave. For example, a component whose frequency is twice the fundamental frequency is called the second harmonic.

INSTANTANEOUS BALLISTIC SPATIAL VECTOR: a three dimensional mathematical entity which represents the magnitude and direction of a force of cardiac origin at any instant during the cardiac cycle which is applied to the body. A spatial force such as this generally has components in the head-foot, side to side and anterior-posterior directions.

LOBE RATIO: the amplitude ratio of sinusoids or waves of a simple harmonic motion or a sine wave.

LOGARITHMIC: a mathematical term which is related to the exponent of that power of a fixed number called the base which equals a given number called the antilogarithm. If a geometric curve is plotted from a logarithmic equation, it is called a logarithmic curve.

LOGARITHMIC DECREMENT: a logarithmic curve which diminishes with respect to time.

MICROFARAD: a farad is the electrical term which expresses the capacity of a condenser for storing an electrical charge. A microfarad is one millionth of a farad. The farad is too large a value to be applied to the usual electrical condenser and avoid fractional numbers.

MAGNETIC TRANSDUCER: a device which changes mechanical movement into electricity by means of relative motion between a magnetic field and a coil of wire.

NATURAL FREQUENCY: the frequency of vibration or oscillation of a vibratory system at which resonance exists. The unit of measurement is the cycle per second.

OVERDAMPING: when a force is suddenly applied to an overdamped vibratory system, the system will deflect and consume more time in reaching its destination than if the system were critically damped.

PHASE SHIFT: the displacement in degrees between two waves of the same frequency. For example, if a vibratory system is excited by a sinusoidally varying force and the resulting deflection is also sinusoidal or simple harmonic motion, and if a displacement or lag exists between the deflection and the applied force or the two sinusoids, the lag measured in degrees is the phase shift.

PHOTOELECTRIC TRANSDUCER: a device which converts light energy into equivalent electrical energy.

PIEZOELECTRIC TRANSDUCER: a device which converts mechanical force into electricity by flexing a crystal made of material such as rochelle salt, barium titanate or quartz.

RESONANT FREQUENCY: same as natural frequency.

RESONANCE: occurs whenever there is impressed upon a body the frequency at which it would vibrate if set in motion and then left to itself.

RESPIRATORY WEAVE: when a ballistocardiograph is sensitive to the very low frequencies which make up the pneumogram, a pneumogram will be superimposed upon the ballistocardiogram. The slowly changing pneumographic pattern is called the respiratory weave.

SPATIAL BALLISTIC FORCE VECTOR: A three dimensional mathematical entity which represents the magnitude and direction of a force of cardiac origin which produces body movement in a ballistocardiographic sense.

SINUSOIDAL OSCILLATION: a vibration which is simple harmonic motion. When the magnitude of the oscillation is plotted in the form of a graph against time, the resultant curve is a sine wave. An example of such motion is the movement of a pendulum.

TIME CONSTANT: a mathematical term which represents the rate of charge or discharge of a condenser through a resistance. The larger the condenser and/or the resistance, the larger will be the time constant.

TRANSDUCER: a device designed to receive energy such as mechanical and convert it into equivalent energy of another form such as electrical. A microphone is a transducer, because, by means of it, acoustic energy is transformed into equivalent electrical energy.

UNDAMPED NATURAL PERIOD: equal to two times the deflection time of a vibratory system such as a ballistocardiograph table when a force is instantaneously applied.

UNDERDAMPED: when a force is instantaneously applied to an underdamped vibratory system, the system will deflect and overshoot its destination and then return to its destination.

VELOCITY BALLISTOCARDIOGRAM: a graphic representation of the speed with which the body moves as a result of the forces produced by cardiac action when recorded with respect to time.

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Phenolic Compounds in the Treatment of Rheumatic Fever

I. A Study of Gentisic Acid Derivatives

By NORMAN E. CLARKE, M.D., ROBERT E. MOSHER, PH.D., AND CHARLES N. CLARKE, M.D.

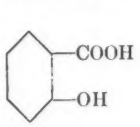
The chemical compounds known to suppress the manifestations of rheumatic fever are reviewed and the antirheumatic nature of certain phenolic compounds discussed. We report on 75 patients with acute rheumatic fever who have been treated with gentisate compounds and discuss the records of 44 of these patients who have been followed for 3 to 20 months after discontinuing drug therapy. These patients were treated with sodium gentisate, "Gen," methyl cellulose-sodium gentisate and gentisic acid ethanolamide. The urinary excretion records of these drugs are given with selected blood level studies. The antihyaluronidase effect of salicylic acid metabolites and the relationship of these phenolic compounds to the pituitary-adrenal axis are discussed.

THE chemical compounds known to suppress the manifestations of rheumatic fever are phenolic acid derivatives and the hormones cortisone and adenocorticotropic hormone (ACTH). These hormones have shed light on the pathogenesis of this disease but added little to our hope for better rheumatic fever therapy. Cortisone and adrenocorticotropic hormone are most effective in the severe form of acute rheumatic fever,[3-12] but in general, their therapeutic results have been less satisfactory than those of salicylates[1, 2, 5, 6, 8, 11, 12]; the disease's manifestations recur when the hormones are stopped[4, 5, 9, 10, 11] and the effect on carditis and valvular damage is of doubtful value.[8-12] The monophenolic salicylates continue to be regarded as the most generally effective and practically useful form of rheumatic fever therapy and can be used to differentiate rheumatic fever from other diseases which have similar symptomatology.

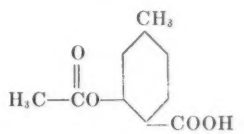
It is significant that since the salicylates were introduced 75 years ago,[13] they have not been replaced in the treatment of rheumatic fever. The salicylates are but one of several phenolic acid compounds that have antirheumatic properties. It has been demonstrated[14] that the monophenolic o-cresotinic acid is effective in rheumatic conditions, but others[15-16] have found this drug inferior to the salicylates. The m-cresotinic acid has an effect similar to that of sodium salicylate.[16] A decoction of bilberry leaves, a constituent of which is the diphenolic hydroquinone, has been used in the treatment of rheumatism[17] and also the acetyl derivative of m-cresotinic acid or amatin,[18] which is tolerated by man up to 3 Gm. daily with good analgetic and antipyretic action and without it causing gastric irritation or marked perspiration. The drug salicyl resorcinol[19] has been used for the treatment of rheumatism, and acute rheumatic fever manifestations are suppressed by gamma resorcylic acid, but the meta and parahydroxybenzoic acids are inactive.[20] The phenolic compounds known to suppress some or all of the manifestations of rheumatic fever in the human have the following structures.

Monophenols

Salicylic acid



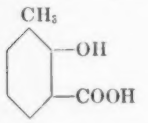
Amatin



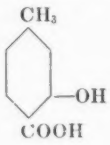
From the Department of Research, Providence Hospital, Detroit, Mich.

The "Gen" used in this study was supplied through the courtesy of Edwin L. Gustus, Chicago, Ill., the gentisic acid ethanolamide by The Panray Corporation, New York City, the sodium gentisate tablets and sodium gentisate–methyl cellulose compound by Sutliff & Case Company, Inc., Peoria, Ill., and the Benemid by Sharpe & Dohme, Inc., Glenolden, Pa.

O-cresotinic acid

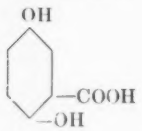


M-cresotinic acid

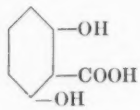


Diphenols

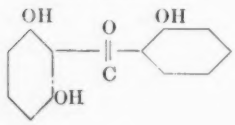
Gentisic acid



Gamma resorcylic acid



Salicyl resorcinol



The structures of these compounds show certain common features which may account for their antirheumatic action. They all contain an aromatic ring (and aromatic acids as a group are antiseptic without being toxic in man, a property practically unique), they are unstable in the body and have antipyretic and analgesic properties. All of these compounds have one carboxyl group and, with the exception of amatin, have one or more hydroxyl groups, with a hydroxyl group adjacent to the carboxyl group, a relationship which is probably of biochemical and therapeutic importance.[21-39] No conclusion, as yet, can be drawn concerning the position that the second hydroxyl group must occupy or whether this second group must necessarily be of a phenolic nature. The introduction of a carboxylic group into the phenolic ring attenuates the toxic action of a phenol, especially when it occupies the meta or para position, and it increases the antiseptic action when it occupies the ortho position.[21]

There is little known about the mechanism of the action of these drugs or compounds, but it probably is due to one or more of the following properties. Many phenolic acid derivatives have (1) antihyaluronidase or limiting capillary diffusion action, (2) a blocking action on systems, due to their oxidation-reduction properties, (3) some bactericidal or bacteristatic action, (4) an antimitotic influence, (5) perhaps an action of an adrenocortical nature mediated through pituitary stimulation or the provision of building blocks for the adrenal cortex and (6) probably some effect on allergic processes due to their ability to precipitate or combine with certain proteins. The orthohydroxy benzoic acids form highly colored complexes with a number of heavy metals and this property may cause stronger bindings to proteins. The first, second, fifth and sixth characteristics of phenols seem of greatest importance in rheumatic fever therapy in the light of our present knowledge.

The demonstration by Guerra[22] that salicylate inhibits the activity of hyaluronidase in vivo but not in vitro suggested that this action might be due to a metabolite formed by the organism and it was found[23] that gentisic acid is a metabolite of salicylic acid.

Since the successful use of sodium gentisate in five patients with acute rheumatic fever by Meyer and Ragan[24] in 1948, Ory[25] and his coworkers in Brussels and Camelin[26] and his group in France have found sodium gentisate to be as therapeutically effective in rheumatic fever as the salicylates and to produce few if any toxic effects. Gorsuch[27] believes that the therapeutic efficiency of sodium gentisate is greater than that of the salicylates, particularly its analgesic and antipyretic action. Testoni and Strano[28] compared sodium gentisate with salicylates and found that sodium gentisate was equal, if not superior, to salicylates in the treatment of rheumatic fever, while Schafer and Rashkoff,[29] after comparing sodium gentisate and salicylates, concluded that sodium gentisate controlled the clinical manifestations of rheumatic fever as promptly and effectively as salicylates and did not produce any toxic symptoms, prolongation of prothrombin time, changes in the blood count nor changes in liver or kidney function. Boyd[30] has treated 80 patients with various arthritic diseases with a combination of sodium gentisate and salicylates and with salicylates alone and found that the gentisate was remarkably free of toxic effects. After comparing sodium salicylate with sodium gentisate, Caprette[31] concluded that the salicyl-

ate was more effective than sodium gentisate in acute articular rheumatism.

We have treated 75 patients having acute rheumatic fever with gentisic acid compounds and have followed 44 of these patients for from 3 to 20 months since discontinuing the drug. These 44 patients are equally divided into 22 patients who had a primary and 22 patients who had a recurrent attack of rheumatic fever.

Observations

Results of Treatment with Sodium Gentisate

A tablet or the powdered form of sodium gentisate, put up in capsules or in a liquid vehicle, was administered to 13 patients who had a primary attack of rheumatic fever. The drug was given for from 60 days to 6 months, with a starting schedule of 1.0 or 1.2 Gm. of sodium gentisate every three or four hours day and night. As improvement occurred, the amount of drug was gradually reduced to a minimum of 1.2 Gm. every four hours four times daily. Some of these patients obtained symptomatic relief within 24 hours after the sodium gentisate therapy was started, a few in four weeks, but most of these patients were symptom free within the first two weeks of treatment. Symptomatic relief occurred earlier in those patients who had the more severe form of rheumatic fever and who had the highest sedimentation rates. The temperature and heart rate became normal within two to three weeks and the sedimentation rate was normal in one to six weeks or in an average of four weeks. The only toxic reaction observed was nausea in two children, but when the sodium gentisate was given in a liquid vehicle the nausea promptly disappeared.

We have attempted to evaluate the degree of cardiac damage in these patients in whom gentisate treatment has been discontinued for from 3 to 15 months. Of 13 patients, a heart murmur was not heard in seven, and in 11 of these patients there was no evidence of heart enlargement; one patient had had a recurrence of rheumatic fever.

Fifteen patients who had a recurrent attack of rheumatic fever were given 5.2 to 10.4 Gm. of sodium gentisate every 24 hours, with most of them receiving 8.0 Gm. of the drug each day or 1.0 Gm. of sodium gentisate every three hours, day and night; this was decreased as improvement occurred. The drug was given for from 1 month to 24 months but most of these patients were treated for an average of six months. We found it necessary to continue sodium gentisate treatment for a longer time in the recurrent type of rheumatic fever, particularly in several patients who were in older age groups. Two of our patients with persistent rheumatic fever have required continuous therapy for 20 and 22 months to remain symptom free. There was complete relief of symptoms in from 24 hours to 3 weeks following sodium gentisate therapy with an average of 11 days. The blood sedimentation rate returned to normal in from 30 to 120 days with an average of 60 days for 13 of these patients. The disease manifestations have recurred in two of these patients, but 12 patients have remained symptom free for an average of eight months since sodium gentisate treatment was discontinued.

An attempt to evaluate increased cardiac damage in 13 patients after therapy had been discontinued for 3 to 20 months has shown the heart findings unchanged in six, the murmurs decreased in six, with an aortic diastolic murmur, previously present, absent in one; one patient has died.

We have found sodium gentisate to be more generally satisfactory than the salicylates in the treatment of the acute, recurrent and persistent forms of rheumatic fever, but it has two disadvantages. (1) Sodium gentisate is rapidly eliminated from the body, which requires that it be administered at frequent intervals throughout the entire day, and (2) the sodium content detracts from its use in patients with rheumatic heart disease and active carditis who are in a state of congestive heart failure. We have sought to overcome these defects of sodium gentisate in groups of patients treated with special compounds of gentisic acid.

Results of Treatment with "Gen"

Sodium gentisate was combined with a non-absorbable, innocuous acid-absorbing resin to determine whether the speed of hydrolysis in the gastrointestinal tract could be retarded.

Such a combination, prepared under the trade name "Gen," was given to two patients who had primary attacks and to three patients who had recurrent attacks of rheumatic fever; the latter patients were in congestive heart failure. These patients received 1.0 to 1.2 Gm. of Gen every three or four hours day and night. In one patient who had a primary attack of rheumatic fever, the drug had to be discontinued after four weeks of therapy because of poor response. The second patient who had a primary attack of rheumatic fever required nine months of treatment with Gen before the rheumatic fever manifestations were suppressed. Of the three patients who had recurrent rheumatic fever and who were in congestive heart failure, one showed a minimal reduction in the rheumatic fever manifestations and gradual progression of the congestive heart failure, the Gen being discontinued after six weeks. The other two patients with congestive heart failure were relieved of their rheumatic fever manifestations, but they showed no corresponding improvement of their congestive heart failure which had to be corrected by digitalization and diuretics. The temperature, heart and sedimentation rates were influenced much more slowly with Gen than with sodium gentisate.

Our experience with Gen caused us to believe that this compound reduces the effect of sodium gentisate and that the use of an anion resin in combination with sodium gentisate does not improve the absorption of gentisic acid from the gastrointestinal system nor aid in the treatment of rheumatic fever patients who are in a state of congestive heart failure.

Results of Treatment with Methyl Cellulose–Sodium Gentisate

It is claimed that methyl cellulose delays the absorption of a digitalis glycoside from the gastrointestinal tract and prolongs the effect of the drug.[32] We have investigated this effect with a tablet combination of 0.3 Gm. of sodium gentisate and 0.09 Gm. of methyl cellulose. In vitro studies with these tablets had demonstrated that disintegration in gastric and intestinal juices required twice the time for that of regular sodium gentisate tablets. Of six patients treated with methyl cellulose–sodium gentisate tablets, four had a primary and two a recurrent attack of rheumatic fever. Two of these patients were symptom free after four days of treatment, the maximum was two weeks and the average was one week. The sodium gentisate–methyl cellulose therapy was continued for from four weeks to three months, with all of these patients receiving 8.0 Gm. of methyl cellulose–sodium gentisate every 24 hours or 1.2 Gm. every three hours from 7 a.m. to 10 p.m. which avoided interrupting their sleep. The temperature of these patients became normal in an average of six days, and the heart rate was normal in an average of three weeks after therapy was instituted. The blood sedimentation rate became normal within 12 days to six weeks after methyl cellulose–sodium gentisate treatment was started with an average of 28 days. There were no toxic reactions.

An attempt to evaluate heart damage three months after therapy had been discontinued showed the heart size normal in the four patients who had had primary attacks of rheumatic fever and the heart enlargement unchanged in the two patients who had had recurrent attacks of the disease. The heart murmurs persisted in all patients but in those who had primary attacks of rheumatic fever the murmurs were considerably decreased in intensity. Because of the sodium content, sodium gentisate–methyl cellulose is not satisfactory for patients who are in congestive heart failure but it does permit the use of smaller amounts of drug and it need be given less often, its action being more sustained with lower urinary minute output.

Results of Treatment with Gentisic Acid Ethanolamide

Five patients who had acute rheumatic fever were treated with gentisic acid ethanolamide. The ethanolamide of gentisic acid has been known for several years and has been used as a solubilizing agent for vitamins. No work had been done to evaluate this salt in the treatment of acute rheumatic fever. We were interested in its therapeutic possibilities but particularly for patients with acute rheumatic fever who were

in congestive heart failure. Acute toxicity studies with gentisic acid ethanolamide in mice, rats and rabbits had shown that it was of much lower toxicity than was sodium salicylate. Chronic toxicity studies in young rats who received daily subcutaneous injections of gentisic acid ethanolamide in doses of 100 mg. per kilogram, and 300 mg. per kilogram, for four weeks, had shown no adverse influence on the growth rate or blood picture. The microscopic examination of hearts, livers, kidneys, spleens and femoral bone marrows revealed no pathologic changes.[33] Of the five patients treated, three had a primary and two a recurrent attack of rheumatic fever. All of these patients obtained complete symptomatic relief after two to five days of treatment with 1 Gm. of the drug given every three hours, six times daily, or a total of 6.0 Gm. of gentisic acid ethanolamide in 24 hours. The drug was administered for from 40 to 66 days. The temperature of these patients became normal within 5 to 12 days and the heart rate was normal within 7 to 16 days after gentisic acid ethanolamide therapy was started. The blood sedimentation rate became normal after 12 to 44 days of therapy or an average of 25 days.

These five patients have been examined from four to five months after therapy was discontinued and all have shown a distinct reduction or change in the intensity and character of their former heart murmurs and the heart size has remained normal or unchanged. The state of congestive heart failure that was present in one of these patients was corrected with the suppression of the rheumatic fever, and a similar result has been observed in two other patients who have been followed for less than three months since the drug was discontinued. This limited experience suggests that gentisic acid ethanolamide has qualities which make it superior to sodium gentisate in the treatment of acute rheumatic fever. The gentisic acid ethanolamide therapy gave earlier symptomatic relief and the decline to normal of the temperature and pulse rate was more consistent and somewhat earlier than with sodium gentisate. The gentisic acid ethanolamide suppresses the manifestations of rheumatic fever with less drug than does sodium gentisate and the absence of sodium makes it desirable for patients who are in congestive heart failure.

Action on Lymphocytes

Of the 44 patients who had acute rheumatic fever and who were treated with compounds of gentisic acid, 39 had an average rise of 54 per cent and four patients had a distinct fall in their lymphocyte counts. The elevation of the lymphocyte counts occurred within the first 10 days after gentisate therapy had been started and later the lymphocyte counts gradually returned to their former or even lower levels. In some patients, and usually in the latter part of their illness, there was a secondary rise in the lymphocyte counts. An increase of 52 per cent in the lymphocyte count occurred within an average of nine days in 10 patients with acute rheumatic fever whom we treated with sodium salicylate.

Absolute Eosinophil Counts

Absolute eosinophil counts were obtained frequently on 23 patients. A more than 50 per cent decline in the absolute eosinophil count was observed in these patients within the first 10 days of gentisate therapy. In most of these patients the greatest decline in the absolute eosinophil count was observed on the sixth or seventh day of gentisate therapy. The absolute eosinophil count dropped from 250 and 800 eosinophil cells to zero cells in three patients after seven days of gentisate therapy and after nine days in another patient.

The Urinary Excretion of Gentisic Acid Compounds

Chemically speaking the gentisates are derivatives of 2,5-dihydroxybenzoic acid, and clinical experience had indicated that they were rapidly eliminated from the body. To determine the rates of elimination, the 24 hour urinary outputs were analyzed for the uncombined drug (table 1). The excretion of gentisic acid was not influenced by variations in the total urinary output unless the amount of urine was greatly limited. When this occurred, on the following day there was always an increased urinary output which compensated for the decrease of the previous day. The

different urinary pH levels had no influence on the amount of gentisate excreted.

If we consider only the uncombined form of the drug, the ethanolamide of gentisic acid is excreted to a lesser extent than is the sodium gentisate or gentisic acid, a difference that is statistically significant. The excretion of gentisic acid ethanolamide in children is greater

TABLE 1.—*Excretion of Gentisic Acid Compounds per 24 Hours*

Drug	No. of Patients	No. of Samples	Aver. 24 hr. Excretion* %	Standard Deviation
Sodium gentisate	8	28	58.3	± 14.8
Gentisic acid	4	16	60.9	± 18.1
Gentisic acid ethanolamide† (adults)	3	19	25.8	± 6.3
Gentisic acid ethanolamide† (children)	3	29	44.1	± 11.1

* None excreted in stool.
† Excretion of uncombined form.

TABLE 2.—*Excretion of Gentisic Acid Compounds with Retarders per 24 Hours*

Drug	No. of Patients	No. of Samples	Aver. 24 hr. Excretion* %	Standard Deviation
Sodium gentisate on anion resin	5	33	58.4	±25.5
Sodium gentisate & methyl cellulose	4	30	61.7	±13.9
Gentisic acid† ethanolamide and Benemid (adults)	2	12	35.5	±5.9
Gentisic acid† ethanolamide and Benemid (children)—	5	37	23.5	±9.5

* Uncombined form of drug.
† Benemid: Adults, 2 Gm. per 24 hours; Children, 1 Gm. per 24 hours.

than in adults, while the 24-hour excretion of gentisic acid and sodium gentisate is approximately the same.

In table 2 is given the 24-hour urinary output of gentisic acid when sodium gentisate has been combined with an anion resin or with methyl cellulose and of gentisic acid ethanolamide given with Benemid as a retarding agent.

The adsorption of sodium gentisate on an anion resin does not decrease the amount of gentisate that is excreted through the urine in 24 hours. The same is true for the combination of sodium gentisate and methyl cellulose. The excretion of gentisic acid ethanolamide with Benemid in children and adults appears confusing, but we have tabulated only that portion of the drug that is excreted in the free or uncombined state. The apparent difference in excretion between the sodium gentisate and the gentisic acid ethanolamide is due to a greater conjugation of the latter compound. This explanation is at least supported by the data shown in table 3.

TABLE 3.—*Excretion of Conjugates of Gentisic Acid Compounds*

Drug	No. of days	Daily drug Intake (millimols)	Aver. output of Ethereal sulfur (millimols)	Aver. output of Glucuronic acid (millimols)
Sodium gentisate	14	34	3.0	0.8
Gentisic acid ethanolamide	34	32	6.0	9.0
None	5	none	1.0	0.5

TABLE 4.—*Blood Levels during a Four-Hour Period between Treatments*

	Blood levels in mg. per cent				
Drug	0 time	30 min.	1 hour	2 hour	4 hour
Sodium gentisate	2.0	9.8	8.0	7.0	2.0
Sodium gentisate; methyl cellulose	6.0	4.0	5.0	5.5	6.0
Sodium gentisate with an anion resin	2.1	2.1	2.4	4.2	2.1

These data do not permit a final answer as to the degree of conjugation of these various gentisic acid compounds but it indicates that a great difference does occur. The combination of gentisate compounds with the retarder, Benemid, does not affect the excretion of the free drug but definitely lowers the total excretion of gentisates. We have found, however, that the retarding action of Benemid on the total excretion of a gentisate may be lost after 10 days to two weeks.

Blood Levels of Certain Gentisic Acid Compounds

The gentisic acid compounds suppress the manifestations of rheumatic fever at lower blood levels than are required for the salicylates. A blood level of 3.5 to 5 mg. of gentisic acid per 100 cc. is sufficient to suppress the manifestations of rheumatic fever. Table 4 gives the blood levels of patients receiving 1.0 Gm. of a gentisic acid compound every four hours with zero hour being just before the drug was given.

The combining of sodium gentisate with methyl cellulose retards the breakdown of the tablet in the gastrointestinal tract and produces a more constant and prolonged absorption of the gentisate into the blood stream as compared with the rapid and high absorption and rapid excretion which occurs with sodium gentisate and the limited absorption of sodium gentisate when combined with an anion resin. The total 24-hour urinary output of gentisate is the same for the three gentisate compounds.

We avoided the use of vitamin C with the gentisates so that we might obtain a single drug action on the rheumatic fever patient. This may account for some of the differences in our findings and those reported for other antirheumatic agents.

Discussion

The metabolites of the salicylic acid are probably the substances which act to suppress the manifestations of rheumatic fever in patients receiving salicylate therapy. A mixture of the salicylic acid metabolite, gentisic acid, and hyaluronidase is inactive, but when such a mixture is incubated it becomes an active inhibitor of the depolymerization of hyaluronic acid by hyaluronidase.[34] By means of the turbimetric method, it has been demonstrated[35] that many other aromatic or phenolic compounds are inhibitors of hyaluronidase. The gentisic acid in the body is at least partially converted to the quinone form. It has been found by in vitro studies that the depolymerization of hyaluronic acid by hyaluronidase is inhibited by the quinone of gentisic acid or 2,5-benzoquinone carboxylic acid at a concentration of 0.001 M and higher.[36] We have observed that an impure form of gentisic acid (90 per cent purity) was more effective in acute rheumatic fever patients than was a highly purified form of the drug. This is due to the presence of small amounts of the isomers of gentisic acid (side products of the synthesis of gentisic acid) or of the oxidized form of gentisic acid. The nonspecific hyaluronidase inhibitor in human serum appears to be a homogeneous complex of heparin, polypeptide and lipid which migrates with the albumin,[37] while that which inhibits streptococcal hyaluronidase migrates entirely with the gamma globulin, is not heat-labile and is a true neutralizing antibody.[38] The known property of certain phenols to combine with or precipitate proteins and to block enzyme systems may account for their antihyaluronidase behavior and this ability varies with different phenolic compounds.

The antirheumatic action of salicylates and other phenolic derivatives may be mediated through the pituitary-adrenal axis and be more specific than has been formerly supposed. The specific action of certain phenolic compounds in rheumatic fever may be explained by the "accomplished ability to convert salicylic acid 'in vitro' to diphenic acid and thence to members of the steroid group and the direct action of salicylic acid upon cholesterol and/or cholesteryl esters to influence the concentration of the sterol and its esters and the ratio between the free cholesterol and the cholesteryl ester fraction" as suggested by Tormey and Barnhurst.[39] The inherent inability of the rheumatic fever patient to demobilize the antihemolytic agent cholesterol after a hemolytic attack causes it to be partially demobilized abnormally through conversion to excess desoxycorticosterone.[40] It has been shown that desoxycorticosterone can produce the characteristic changes of rheumatic fever.[41]

The amount of ascorbic acid in the suprarenal glands is a measure of the glands' activity, and the removal of ascorbic acid from the adrenal gland is under the control of adrenocorticotropic hormone. The giving of preliminary treatment with the adrenal cortical hormone prevents the normal depletion of ascorbic acid by pituitary and adrenal gland activity. The agents which stimulate the adrenocorticotropic hormone-adrenocortical ac-

tivity probably do so by diminishing the concentration of the adrenal cortical hormone in the blood or by increasing its utilization by the tissues.[42] It has been demonstrated in rats[43] that salicylates cause a definite depletion of the ascorbic acid content of the adrenal glands, the degree of depletion being proportional to the amount of the drug that has been given. This response does not occur in hypophysectomized rats and tends to be inhibited by preliminary treatment with Cortone. In another study with rats,[44] the subcutaneous injection of 400 mg. per kilogram of sodium salicylate produced a pronounced decrease in the ascorbic acid content of the pituitary and adrenal glands which persisted for more than 24 hours. The injection of 0.2 mg. of adrenaline (per rat) produced a similar but less marked effect.

There is a regular and increased excretion of reducing steroids but no regular effect on the excretion of the neutral 17-ketosteroids in humans with rheumatic diseases who are treated with acetyl salicylic acid, but there is no direct relationship between the amount of the reducing steroids excreted and the type of rheumatic disease but each increase in the excreted reducing steroids corresponds to the patient's clinical improvement.[45] A single intraperitoneal injection of a large dose of salicylate into intact rats produced the biochemical, histologic and hematologic picture of stress. After the injection of sodium salicylate into hypophysectomized rats, no significant change was observed in the ascorbic acid or cholesterol content of the adrenal glands nor was there an important decrease in the number of circulating eosinophils. Adrenocorticotropic hormone did produce significant biochemical and hematologic changes in the hypophysectomized rats similar to those observed in intact rats.[46] The integrity of the pituitary-adrenal axis may be essential for effective therapy with phenolic acid derivatives, and where adequate salicylate therapy has been ineffective, as in malignant rheumatic fever, perhaps the hypothalmic-pituitary-adrenal axis has been seriously damaged by the disease.

The reduction of circulating eosinophils by 50 per cent or more after the injection of a fixed amount of adrenocorticotropic hormone proves the integrity of the pituitary-adrenal axis.[47] The administration of salicylates produces a more than 50 per cent eosinopenia[48] in guinea pigs and also in man.[49] Others[50] have been unable to demonstrate eosinopenia in normal humans in whom plasma salicylate concentrations, usually regarded as necessary, had been attained. A review[51] of this negative experience has shown that after a single oral dose of 4 or 6 Gm. of sodium salicylate there is no significant decrease in the absolute eosinophil count during the first four hours, but a significant drop occurs between the fourth and sixth hour due, undoubtedly, to the slow absorption from the intestinal tract. The urinary uric-acid–creatinine ratio increased significantly by the second hour. A positive Thorn test has been observed four hours after an intravenous injection of 4 Gm. of sodium salicylate.[50] The pronounced eosinopenia and increase in the uric acid-creatinine ratio are associated with oversecretion of adrenocorticotropic hormone or Cortone, as is the increased urinary excretion of neutral steroids. The salicylates, given in adequate doses, produce these several changes which depend on stimulation of the adrenal cortex by the pituitary gland. In patients whom we have treated with a compound of gentisic acid, we have observed a greater than 50 per cent reduction in the absolute eosinophil count within the first 10 days of therapy and in four patients the eosinophile cells were reduced to zero.

A decrease in circulating lymphocytes has been considered to be a sensitive indicator of extra quantities of adrenocorticotropic hormone or adrenal cortical factors in the blood stream.[52, 53] A significant drop in the lymphocyte count with adequate salicylate therapy has been observed[54] and been attributed to stimulation of the pituitary production of adrenocorticotropic hormone. This action of salicylates on the lymphocyte count is contrary to our experience with patients whom we have treated with salicylates and with the gentisic acid compounds. We observed, usually, a definite rise in the lymphocyte count and within 10 days after salicylate or gentisate therapy had been started.

Of 75 patients, 44 of whom have been ob-

served 3 to 20 months after discontinuing treatment with compounds of gentisic acid, we have found that the gentisates are the equal and in some respects are superior to other forms of therapy in suppressing the acute manifestations of rheumatic fever. The return to normal of the temperature and blood sedimentation rate was earlier with sodium gentisate, gentisic acid ethanolamide and methyl cellulose–sodium gentisate than with salicylates. Most patients treated with these gentisate compounds had normal temperatures in an average of six days and normal blood sedimentation rates in an average of 27 days. The 10 patients with acute rheumatic fever whom we treated with sodium salicylate had normal temperatures in an average of 14 days; others have reported an average of 6.6 days for patients treated with oral and intravenous salicylates.[56] The blood sedimentation rate was normal in an average of 30 days[55] and 54.1 days[56] in other groups of patients with acute rheumatic fever who were treated with the salicylates.

The salicylates are not tolerated by children with the gastrointestinal symptoms of acute rheumatic fever but these patients do tolerate the gentisates. Unlike the salicylates, the gentisates cause no disagreeable or harmful reactions. The gentisates relieve the manifestations of the persistent and cerebral forms of acute rheumatic fever and are well tolerated for many months. We were unable to determine whether these drugs shorten the normal course of the disease. In the 44 patients in whom treatment had been discontinued for from 3 to 20 months, the disease recurred in three patients.

The rapid and complete elimination from the body of sodium gentisate, which necessitates administering this drug at frequent intervals, was materially modified by the use of gentisic acid ethanolamide or a combination of sodium gentisate with methyl cellulose. We believe that the superiority of gentisic acid ethanolamide results from the slower breakdown and utilization of this compound in the body. The combining of sodium gentisate with methyl cellulose delays the absorption of the gentisate from the gastrointestinal tract, for while the 24-hour excretion of the gentisate fraction is the same as with sodium gentisate, the therapeutic blood level was maintained more constantly.

We have observed no important toxic reactions from the gentisates among the 75 patients whom we have treated, and we have given up to 6.0 Gm. in a single dose and as much as 5.2 Gm. a day for as long as 24 months. The two patients who received the drug in capsule form and who complained of nausea were given prompt relief when the gentisate was administered in a liquid vehicle.

Summary

The general nature of phenolic acid compounds in the treatment of rheumatic fever has been discussed.

Of 75 patients treated with gentisate compounds, we have discussed 44 who have been observed for from 3 to 20 months after the drug had been discontinued.

The metabolism of salicylic acid in the human body and the therapeutic importance of its metabolites, and, in particular, of gentisic acid, have been reviewed.

The clinical and partial laboratory results have been presented for 28 patients who were treated with sodium gentisate, for five patients who were treated with a combination of sodium gentisate with an anion resin, for six patients who were treated with a combination of sodium gentisate and methyl cellulose and for five patients who were treated with gentisic acid ethanolamide.

It is our impression that gentisate compounds are more effective than other forms of rheumatic fever therapy in suppressing the manifestations of rheumatic fever.

The superior tolerance for the gentisates is impressive and makes the treatment of rheumatic fever easier for the doctor and the patient.

The methyl cellulose–sodium gentisate compound and gentisic acid ethanolamide showed slower absorption or utilization within the body and the sodium gentisate–methyl cellulose compound maintained the most constant therapeutic blood levels.

The gentisates cause a pronounced rise in the lymphocyte count rather than the reduced lymphocyte count observed with cortisone and

adrenocorticotropic hormone therapy. We purposely chose to not use vitamin C in conjunction with the gentisates so as to obtain a single drug response.

A relationship between salicylic acid or its metabolite, gentisic acid, and the corticoadrenal axis in acute rheumatic fever has been discussed.

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Sumario Español

Los compuestos químicos conocidos como supresores de las manifestaciones de la fiebre reumática son revisados y la naturaleza antireumática de ciertos compuestos fenólicos se discute. Se reporta sobre 75 pacientes con fiebre reumática aguda que fueron tratados con compuestos gentísicos y se discute los records de 44 de los pacientes que han sido observados de 3 a 20 meses después de la droga ser descontinuada. Estos pacientes fueron tratados con gentísato sódico. "Gen," metilo de celu losa-gentisato sódico y etanolamida de ácido gentísico. La excreción urinaria de estas drogas se informa con niveles de sangre seleccionados. El efecto antihialuronidásico del ácido salicílico y sus metabolitos y la relación de los compuestos fenólicos al eje pituitario-adrenal se discute.

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Renal Excretion of Water, Sodium and Chloride

Comparison of the Responses of Hypertensive Patients with those of Normal Subjects, Patients with Specific Adrenal or Pituitary Defects, and a Normal Subject Primed with Various Hormones

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There has long been interest in the possibility that a relationship exists between essential hypertension and those endocrine aberrations that involve the hypothalamus, pituitary and adrenal cortex. This paper represents an attempt to study these relationships indirectly by an examination of the manner in which the kidneys of patients with these various diseases handle water, sodium, and chloride.

ATTEMPTS to hold any one organ responsible for the production of hypertension have been exhaustive but not highly profitable. This might indicate that underlying the hypertension is a generalized systemic reaction in which many organs participate. The hypothalamus, with its protean functions, has recently been suggested as a mediator of this reaction.[1-5] Although this hypothesis should be subjected to experimental investigation, the complexity of hypothalamic function makes any quantative study of its total effect impossible. However, it might be assumed that if the total function is so altered that hypertension results, then each component function must also be altered. The one component function that can be measured is liberation of antidiuretic hormone in response to an appropriate stimulus. In order to measure this, a modification of the technic described by Hickey and Hare[6] has been utilized; it permits comparison of the renal excretion pattern of water, sodium and chloride in a variety of pathologic conditions. The results obtained in hypertensive patients have been compared with those obtained in normal subjects, patients with diabetes insipidus and one patient with Cushing's syndrome.

Since there was striking similarity between the hypertensive patients and the patient with Cushing's syndrome, the study was further extended to determine whether the responses of the hypertensive patients could be reproduced in a normal subject previously treated with desoxycorticosterone acetate (DOCA), Acthar (ACTH), cortisone (Cortone) or cortisone plus pituitrin.

Method

All subjects received a normal unrestricted diet, were in the postabsorptive state, and had been dehydrated for 12 hours. After the bladder had been anesthetized with Metycaine, an indwelling multieyed catheter was inserted into it. Urine was collected for determination of the inulin blank. The urinary output was then measured for three or more consecutive 10-minute periods in order to insure a base line urinary flow of less than 1 cc. per minute, with the obvious exception of those patients with diabetes insipidus. A Lewisohn needle was next inserted into an antecubital vein to permit repeated withdrawal of blood without use of a tourniquet. A blood sample was collected for determination of the inulin and para-amino hippurate (PAH) blanks. A priming infusion of para-amino hippurate and

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inulin was then started, followed by a sustaining infusion calculated to maintain a plasma level of 15 to 20 mg. per cent of inulin and 2 to 3 mg. per cent of para-amino hippurate. Thirty minutes was allowed for equilibration and the experiment was begun. The usual "clearance" procedure was followed except that at the end of each period complete emptying of the bladder was insured by multiple air washings. All blood samples were drawn as closely to the midpoint of the period as possible, and the results were plotted against time on semilogarithmic paper. With the exception of those blood samples used for determination of sodium, heparin was the anticoagulant employed and all samples were immediately centrifuged.

At the conclusion of two to four clearance periods of 15 to 20 minutes each, an intravenous infusion of 2.5 per cent sodium chloride calculated to deliver at the rate of 0.25 cc. per kilogram per minute for 45 minutes was started, and simultaneously the subject began, and completed within 5 to 15 minutes, the imbibition of 20 cc. per kilogram of body weight of water at room temperature. Clearance periods of 15 to 20 minutes were obtained continuously throughout the experiment, which extended for two to three periods after the infusion of hypertonic saline had been discontinued. Thus, in each subject there were from 7 to 11 consecutive clearance periods available for study.

Clearances of inulin and para-amino hippurate were used to determine the glomerular filtration rate and effective renal plasma flow, respectively, according to the principles originally outlined by Smith.[7] All chemical analyses were done in duplicate. Inulin was determined according to Harrison's method as described by Goldring and Chasis.[8] Para-amino hippurate was measured by the method of Smith and associates.[9] The mercurometric titration of the Schaleses[10] was used to determine the chloride content in both the urine and plasma. Serum and urine sodium values were determined by preparing a protein-phosphate-free filtrate, according to the method of Goldzieher and Stone,[11] and then measuring the sodium triple salt, according to the method of Arnold and Pray.[12] Hematocrits were measured in Wintrobe tubes.

The procedure, as outlined, was followed in 10 normal volunteers, eight patients with well documented essential hypertension, one patient with malignant hypertension, two patients with diabetes insipidus and one patient with Cushing's syndrome. In addition, three control clearance periods were performed on two normal subjects and two hypertensive patients in the postabsorptive and hydrated state, for reasons to be discussed later.

One of the normal subjects (E. C.) volunteered for four experiments in addition to the one which has just been described. This permitted him to serve as his own normal control. In the first additional study 5 mg. of desoxycorticosterone acetate (DOCA) were administered intramuscularly the day preceding the experiment, and an additional 5 mg. were given immediately prior to the experiment. After two weeks the same technic was followed except that after two control periods 50 mg. of adrenocorticotropic hormone (ACTH) were rapidly injected intravenously and 50 mg. more were added to the sustaining infusion. One month later the experiment was repeated and 200 mg. of cortisone were given orally two days prior to the experiment, 100 mg. the day preceding the experiment and another 100 mg. the day of the experiment. This study was then repeated in exactly the same manner one month later, except that 0.5 cc. of surgical pituitrin was injected intramuscularly immediately following imbibition of the water.

Results

A complete table and set of graphs was made for each individual experiment. To facilitate presentation of such extensive statistical material, data obtained in only one individual in each group will be presented. Table 1 refers to data obtained on one of the normal subjects, one of the hypertensive patients, one of the two patients with diabetes insipidus, and the one patient with Cushing's syndrome. No correction was made for the Donnan factor, because at a normal plasma protein concentration it is considered to be 1.023 for chloride,[12] and this falls within the range of the experimental error inherent in the determination of glomerular filtration rate. The data for sodium roughly paralleled that for chloride. For the sake of brevity they have not been included in either the tables or discussion.

Several of the columns included in the tables warrant further discussion:

1. *Percentage of Filtered Chloride and Sodium Excreted (Tubular Rejectate).* Taking chloride as an example, we calculated this as the

$$\frac{\textit{clearance of chloride}}{\textit{clearance of inulin}} \times 100$$

or, more simply,

$$\frac{UCl/PCl}{Uin/Pin} \times 100$$

2. *R/P Ratio.* This is a factor used by Hickey and Hare[6] to relate mathematically the concentration of chloride or sodium in the tubular reabsorbate (R) to its concentration in the plasma (P). It is an empiric index of the over-

TABLE 1.

PERIOD	SALINE	Correction for Surface area *	URINE cc/min.	HCT %	R.P.F. cc/min.	G.F.R. cc/min.	F.F.	INULIN U/P	CHLORIDE: PLASMA mEq/L	FILT. mEq/min.	EXCR. mEq/min.	REABS. mEq/min.	H_2O REABS. cc/min.	CLEARANCE cc/min	Cl REABS. mEq/L.	R/P	U/P	%FILT. Cl. EXCR.	%FILT. Cl REABS.	Cl REABS. mEq/100cc. G.F.	WATER: % H_2O EXCR.	% H_2O REABS.
NORMAL SUBJECT (E.C.)																						
1		0.97	0.63	47	728	111	0.15	180.5	110	12.2	0.03	12.2	110.4	0.27	111	1.01	0.39	0.2	99.8	11.0	0.6	99.4
2			0.58	47	654	101	0.15	179.3	111	11.2	0.03	11.2	100.4	0.27	112	1.01	0.52	0.3	99.7	11.1	0.6	99.4
3			0.31	45	335	55	0.16	185.2	116	6.4	0.02	6.4	54.7	0.17	117	1.01	0.63	0.3	99.7	11.6	0.6	99.4
4	■		0.57	43	498	70	0.14	125.7	117	8.2	0.07	8.1	69.4	0.60	117	1.00	1.09	0.9	99.1	11.6	0.8	99.2
5	■		0.91	41	631	81	0.13	92.8	118	9.6	0.14	9.5	80.1	1.19	119	1.01	1.27	1.4	98.6	11.7	1.1	98.9
6			1.20	43	770	121	0.16	104.4	117	14.2	0.18	14.0	119.8	1.54	117	1.00	1.30	1.2	98.8	11.6	1.0	99.0
7			1.27	43	753	122	0.16	99.5	117	14.3	0.22	14.1	120.7	1.88	117	1.00	1.45	1.5	98.5	11.6	1.0	99.0
HYPERTENSIVE PATIENT (H.F.)																						
1		0.86	1.65	42	824	141	0.17	99.3	112	15.8	0.15	15.7	139.7	1.38	112	1.00	0.99	1.0	99.0	9.5	1.0	99.0
2			1.27	43	598	123	0.21	114.5	110	13.6	0.17	13.6	123.6	1.57	110	1.00	1.42	1.2	98.8	9.4	0.9	99.1
3			1.33	43	569	133	0.23	116.7	111	14.9	0.20	14.7	133.0	1.78	111	1.00	1.57	1.3	98.7	9.5	0.9	99.1
4	■		3.80	42	672	150	0.22	46.4	113	17.1	0.65	16.4	148.1	5.79	111	0.98	1.78	3.8	96.2	9.4	2.2	97.8
5	■		6.57	40	753	134	0.18	24.0	116	15.7	1.10	14.6	130.2	9.63	112	0.97	1.72	7.2	92.8	9.3	4.4	95.8
6	■		13.59	38	775	128	0.17	11.0	120	15.5	1.90	13.6	117.3	15.7	116	0.97	1.34	12.2	87.8	9.0	9.1	90.9
7			19.57		685	109	0.16	6.55	122	13.3	2.00	11.4	92.5	18.3	123	1.00	0.99	15.1	84.9	8.9	15.3	84.7
8			19.33	40	709	120	0.17	7.22	116	13.9	1.50	12.5	103.8	12.6	120	1.03	0.77	10.7	89.3	8.9	13.8	86.2
9			10.90	41	564	101	0.18	10.8	116	11.8	1.20	10.6	92.1	10.4	115	0.99	1.13	10.5	89.5	8.9	9.2	90.8
10			8.53	39	675	128	0.19	17.1	114	14.3	1.20	13.1	118.3	10.6	111	0.97	1.45	8.5	91.5	8.9	5.8	94.2
DIABETES INSIPIDUS PATIENT (D.T.)																						
1		0.96	9.47	44	648	108	0.17	11.8	128	13.7	0.24	13.4	98.4	1.87	137	1.07	0.20	1.7	98.3	12.0	8.5	91.5
2			10.03	45	600	103	0.17	10.7	124	12.8	0.26	12.5	93.1	2.09	134	1.08	0.22	2.1	97.9	11.6	9.3	90.7
3	■		13.00	39	625	112	0.18	8.95	131	14.7	0.46	14.2	99.8	3.51	142	1.08	0.28	3.1	96.9	12.1	11.1	88.9
4	■		15.87	37	689	110	0.16	7.25	135	14.9	0.58	14.3	95.1	4.26	150	1.11	0.28	3.9	96.1	12.5	13.8	86.2
5	■		15.87	37	721	108	0.15	7.11	142	15.4	0.67	14.7	93.2	4.73	158	1.11	0.31	4.4	95.6	13.0	14.0	86.0
6			14.53	38	658	114	0.17	8.18	137	15.6	0.64	15.0	100.3	4.69	149	1.09	0.34	4.2	95.8	12.6	12.2	87.8
7			16.33	39	732	115	0.16	7.34	138	15.9	0.86	15.1	99.6	5.91	151	1.09	0.37	5.0	95.0	12.6	13.6	86.4
8			14.67	39	749	113	0.15	8.05	137	15.6	0.88	14.7	99.2	6.45	148	1.08	0.46	5.7	94.3	12.5	12.4	87.6
PATIENT WITH CUSHING'S SYNDROME (J.D.)																						
1		1.02	1.10	49	286	88	0.31	78.6	109	9.56	0.10	9.46	86.6	0.94	109	1.0	0.79	1.0	99.0	11.0	1.3	98.7
2			0.84	50	299	106	0.35	123.	113	12.0	0.06	11.9	105.3	0.54	113	1.0	0.68	1.6	99.4	11.5	0.8	99.2
3			0.83	50	301	96	0.32	113.	109	10.4	0.07	10.3	95.1	0.65	108	0.99	0.81	0.7	99.3	10.9	0.9	99.1
4	■		4.67																			
5	■		21.4	49	452	112	0.25	5.15	118	13.3	1.56	11.7	90.4	13.23	130	1.10	0.61	11.8	88.2	10.7	19.5	80.5
6	■		27.33	47	463	111	0.24	3.98	122	13.6	2.85	10.7	83.3	23.33	129	1.06	0.84	21.1	78.9	9.8	25.1	74.9
7	■		18.49	47	481	113	0.24	6.00	121	13.7	2.83	10.8	94.4	23.35	115	0.95	1.24	20.7	79.3	9.7	16.7	83.3
8			12.35	48	428	117	0.27	9.30	119	14.0	1.95	12.0	104.7	16.37	115	0.97	1.30	14.0	86.0	10.5	10.7	89.3
9			13.07	48	432	125	0.29	9.36	116	14.6	1.80	12.8	112.1	15.47	114	0.98	1.16	12.4	87.6	10.4	10.6	89.4
10			11.97	49	432	123	0.27	10.1	118	14.8	1.51	13.1	110.2	12.79	119	1.01	1.05	10.4	89.6	10.8	9.9	90.1

* All values except ratios corrected to 1.73 sq. m. of body surface

all tonicity of the tubular reabsorbate with respect either to the plasma or to the glomerular filtrate from which the reabsorbate is derived. It gives no information which its more easily achieved inverse, the U/P ratio, does not supply. It alone cannot serve as an absolute measure of antidiuretic hormone activity unless one assumes that there are no other forces acting to modify the excretion of salt and water.

3. *Amount of Sodium Chloride Reabsorbed per 100 cc. of Glomerular Filtrate.* This is calculated as:

$$\frac{\textit{mEq. sodium or chloride reabsorbed/min.}}{\textit{glomerular filtration rate}} \times 100$$

In general, the effect of an infusion of 2.5 per cent saline was to lower the hematocrit, and to increase the plasma chloride level and

the renal plasma flow. Since there was no consistent effect on the glomerular filtration rate, the filtration fraction tended to fall. Certain specific effects of the infusion of hypertonic saline warrant more detailed analysis:

1. *Effect of Hypertonic Saline on the Inhibition of Water Diuresis*

a. Normal Subjects. The seven normal subjects who simultaneously received the calculated amount of water and hypertonic saline showed almost complete inhibition of normal diuresis. The average maximum urinary output was 3.0 cc. per minute. Subject E. C. in figure 1 represents the typical response of a normal subject.

b. Hypertensive Patients. The hypertensive patients, with one exception, failed to show inhibition of diuresis. The average maximum urinary output in the nine patients was 12.6 cc. per minute, which represents a fourfold increase in the maximum urinary flow of the hypertensive patients as compared with the normal subjects. Patient H. F. in figure 1 represents the typical response of a hypertensive patient.

c. Cushing's Syndrome. Diuresis was also not inhibited in the patient with Cushing's syndrome (fig. 2, patient J. D.). The maximum urinary output reached the high value of 27.3 cc. per minute, a figure surpassed by only one of the hypertensive patients.

d. Diabetes Insipidus. The results obtained on the patients with diabetes insipidus are not strictly comparable, since their base line urinary flows were 10 and 8.5 cc. per minute as compared with a urinary flow of less than 1 cc. per minute in the other three groups. Simultaneous imbibition of water and infusion of hypertonic saline produced a maximum urinary output of 16.3 and 17.5 cc. per minute, respectively. Patient D. T. in figure 2 illustrates the response of a patient with diabetes insipidus.

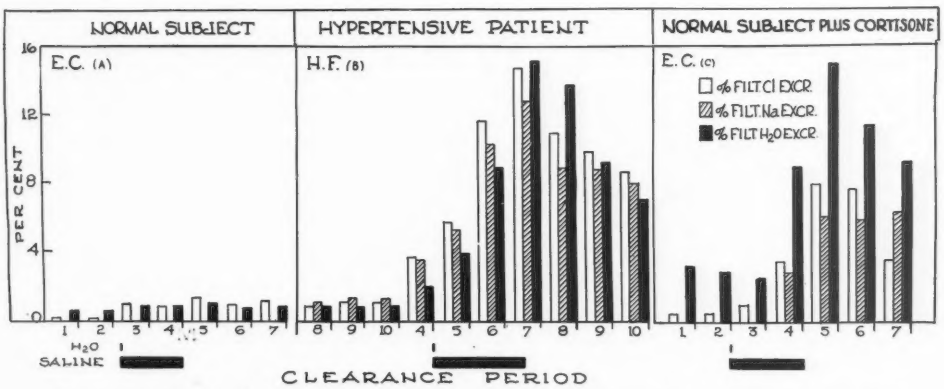

FIG. 1. Comparison of the response of a normal subject, a hypertensive patient and a normal subject primed with cortisone. The cortisone was administered orally in a dosage of 200 mg. two days before, 100 mg. the day before and 100 mg. the day of the experiment. Relationship between the percentage of filtered sodium, chloride and water rejected by the tubules for each collection period is expressed.

2. *Effect of Hypertonic Saline on the Percentage of Filtered Chloride Rejected by the Tubules*

a. Normal Subjects. In the control periods the average percentage of filtered chloride excreted by the tubules was 1.2. Following injection of hypertonic saline, the average maximum was 3.7 per cent. Subject E. C. in figure 1 illustrates this. Only one subject excreted more than 5 per cent of the amount of chloride that was filtered.

b. Hypertensive Patients. With one exception, the hypertensive patients excreted significantly more of the filtered chloride than did the normal subjects. Their control level was 1.4 per cent whereas after injection of hypertonic saline

the average maximum was 10.1 per cent, a figure roughly three times greater than the average maximum of the normal subjects. Patient H. F. in figure 1 illustrates the typical response of a hypertensive patient.

c. Diabetes Insipidus. The average control percentage of filtered chloride excreted was only 1.4. After injection of hypertonic saline this value increased to 5.6 per cent (patient D. T. fig. 2).

d. Cushing's Syndrome. The patient with Cushing's syndrome (patient J. D. fig. 2) showed a control level of 0.7 per cent. Following injection of hypertonic saline she excreted 21.1 per cent of the chloride filtered, by far the maximum observed in any individual patient.

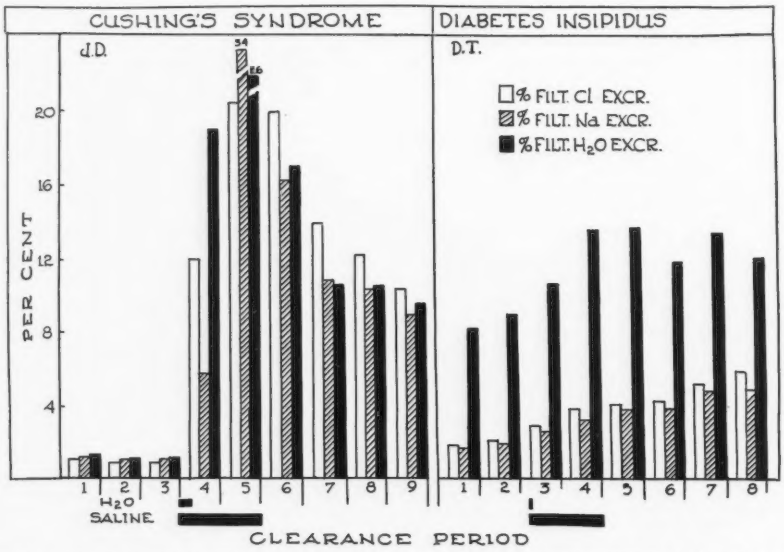

FIG. 2. Comparison of the response of a patient with Cushing's syndrome with that of a patient with diabetes insipidus.

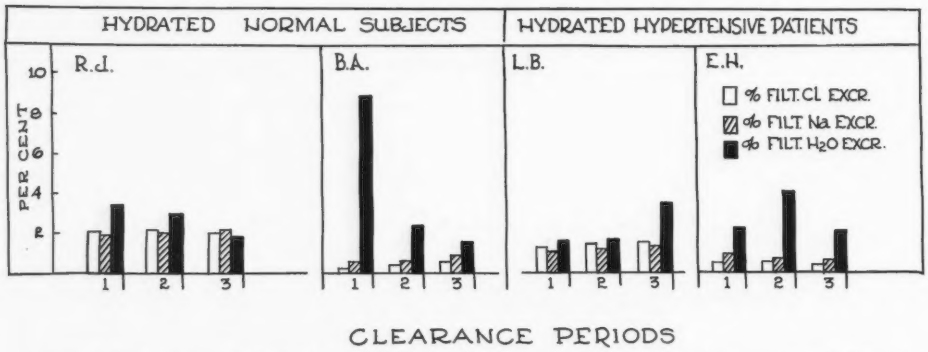

FIG. 3. Illustration of the lack of correlation between urinary output and percentage of filtered chloride and sodium excreted in both hydrated normal subjects and hypertensive patients.

3. *Effect of Hypertonic Saline on the Chloride R/P Ratio and on the Chloride U/P Ratio*

As could be predicted from the urinary output, the chloride R/P ratio in normal subjects

in whom diuresis was inhibited by hypertonic saline tended to be less than 1 in the hyper- when it predictably exceeded 1. At no time did either of the patients with diabetes in-

TABLE 2.

PERIOD	SALINE	Correction for Surface area *	URINE cc/min.	HCT. %	R.P.F. cc/min.	G.F.R. cc/min.	F.F.	INULIN U/P	CHLORIDE: PLASMA mEq/L	FILT. mEq/min.	EXCR. mEq/min.	REABS. mEq/min.	H2O ABS. cc/min.	CLEARANCE cc/min	Cl. REABS. mEq/L.	R/P	U/P	%FILT. Cl. EXCR.	%FILT. Cl. REABS.	Cl. REABS. mEq/100cc. GF.	WATER: % H2O EXCR.	% H2O REABS.
NORMAL SUBJECT (E.C.)																						
1		0.97	0.63	47	728	111	0.15	1805	110	12.2	0.03	12.2	110.4	0.27	111	1.01	0.39	0.2	99.8	11.0	0.6	99.4
2			0.38	47	634	101	0.15	1793	111	11.2	0.03	11.2	100.4	0.27	112	1.01	0.52	0.3	99.7	11.1	0.6	99.4
3			0.31	45	335	55	0.16	165.2	116	6.4	0.02	6.4	54.7	0.17	117	1.01	0.63	0.3	99.7	11.6	0.6	99.4
4			0.57	43	498	70	0.14	183.7	117	8.2	0.07	8.1	69.4	0.60	117	1.00	1.09	0.9	99.1	11.6	0.8	99.2
5			0.91	41	631	81	0.13	92.8	118	9.6	0.14	9.5	80.1	1.19	119	1.01	1.27	1.4	98.6	11.7	1.1	98.9
6			1.20	43	770	121	0.16	104.4	117	14.2	0.18	14.0	119.8	1.54	117	1.00	1.30	1.2	98.8	11.6	1.0	99.0
7			1.27	43	755	122	0.16	99.5	117	14.3	0.22	14.1	120.7	1.88	117	1.00	1.45	1.5	98.5	11.6	1.0	99.0
NORMAL SUBJECT + DOCA (E.C.)																						
1		0.97	0.92	46	564	104	0.18	117.1	113	11.8	0.10	11.7	103.1	0.88	113	1.00	1.00	0.9	99.1	11.3	0.9	99.1
2			0.73	46	457	90	0.20	127.3	113	10.2	0.10	10.1	89.3	0.88	113	1.00	1.18	0.9	99.1	11.2	0.8	99.2
3			0.99	45	527	104	0.20	108.6	116	12.1	0.16	11.9	103.0	1.38	116	1.00	1.18	1.1	98.9	11.4	1.0	99.0
4			1.97	43	794	146	0.18	76.7	118	17.2	0.39	16.8	144.0	3.31	117	0.99	1.68	2.2	97.8	11.5	1.3	98.7
5			2.27	43	624	124	0.20	56.3	120	14.9	0.45	14.4	121.7	3.75	118	0.98	1.66	2.9	97.1	11.6	1.8	98.2
6			2.01	42	527	97	0.18	49.5	118	11.4	0.43	11.0	95.0	3.64	116	0.98	1.81	3.7	96.3	11.3	2.1	97.9
7			2.00	43	610	128	0.21	65.9	119	15.2	0.45	14.7	126.0	3.78	117	0.98	1.89	2.9	97.1	11.5	1.6	98.4
8			2.03	42	615	128	0.21	65.1	119	15.2	0.43	14.8	126.0	3.61	117	0.98	1.80	2.8	97.2	11.6	1.6	98.4
NORMAL SUBJECT + ACTH (E.C.)																						
1		0.97	1.23	48	519	100	0.19	83.0	106	10.6	0.17	10.4	98.8	1.60	105	0.99	1.34	1.6	98.4	10.4	1.2	98.8
2			0.98	48	515	105	0.20	109.7	110	11.6	0.16	11.4	104.0	1.45	110	1.00	1.48	1.5	98.7	10.9	0.9	98.1
3			1.40	44	513	109	0.21	79.9	112	12.2	0.24	12.0	107.8	2.14	112	1.00	1.54	1.9	98.1	11.0	1.3	98.7
4			3.61	44	668	113	0.17	32.5	114	12.9	0.51	12.4	109.4	4.47	113	0.99	1.25	3.8	96.2	11.0	3.2	96.8
5			4.15	44	615	112	0.18	27.8	117	13.1	0.92	12.2	107.9	7.66	113	0.97	1.90	6.8	93.2	10.9	3.7	96.3
6			3.02	45	564	110	0.19	37.5	117	12.9	0.73	12.2	107.0	6.24	114	0.97	2.08	5.5	94.5	11.1	2.7	97.3
7			4.10	44	769	135	0.18	33.9	116	15.7	0.96	14.7	130.9	8.28	112	0.97	2.02	6.0	94.0	10.9	3.0	97.0
8			3.74	46	698	142	0.20	39.0	118	16.8	0.85	15.9	138.3	7.20	115	0.97	1.93	4.9	95.1	11.2	2.6	97.4
9			3.13		658	127	0.20	41.4	118	15.0	0.72	14.3	123.9	6.10	115	0.97	1.94	4.7	95.3	11.3	2.5	97.5
10			2.93		703	131	0.19	45.9	117	15.3	0.69	14.6	128.1	5.90	114	0.97	2.03	4.4	95.6	11.1	2.2	97.8
11			2.00		585	122	0.21	63.0	115	14.0	0.46	13.5	120.0	4.00	113	0.98	2.00	3.2	96.8	11.1	1.6	98.4
12			2.30		629	140	0.22	62.5	114	16.0	0.33	15.5	137.7	4.65	113	0.99	2.02	3.2	96.8	11.1	1.6	98.4
NORMAL SUBJECT + CORTISONE (E.C.)																						
1		0.97	3.90	47	578	107	0.19	28.5	108	11.6	0.04	11.6	103.1	0.37	113	1.05	0.10	0.4	99.6	10.8	3.6	96.4
2			3.00	47	537	100	0.19	34.3	110	11.0	0.05	11.0	97.0	0.45	113	1.03	0.17	0.5	99.5	11.0	3.0	97.0
3			3.30	46	704	132	0.19	41.2	112	14.8	0.18	14.6	128.7	1.45	113	1.01	0.44	1.1	98.9	11.1	2.5	97.5
4			13.50	44	896	148	0.17	11.4	116	17.2	0.66	16.5	134.3	5.69	123	1.06	0.42	3.7	96.3	11.1	9.1	90.9
5			18.13	44	705	116	0.16	6.6	119	13.8	1.14	12.7	97.9	9.58	130	1.09	0.53	8.0	92.0	10.9	15.6	84.4
6			14.47	46	666	126	0.19	9.0	118	14.9	1.17	13.7	111.5	9.92	123	1.04	0.69	7.7	92.3	10.9	11.5	88.5
7			12.63	45	692	123	0.18	10.2	117	14.6	0.66	13.9	112.4	5.64	124	1.06	0.44	4.3	95.7	11.1	10.1	89.9
NORMAL SUBJECT + CORTISONE + PITUITRIN (E.C.)																						
1		0.97	1.20	46	577	95	0.16	81.7	117	11.1	0.23	10.9	93.8	1.97	116	0.99	1.61	2.0	98.0	11.5	1.5	98.7
2			0.86	46	469	80	0.17	93.7	119	9.5	0.19	9.3	79.1	1.60	118	0.99	1.84	1.9	98.1	11.6	1.1	98.9
3			1.70	44	485	128	0.26	77.5	121	15.5	0.41	15.1	126.3	3.39	120	0.99	1.98	2.6	97.4	11.8	1.5	98.7
4			2.13	42	640	128	0.20	61.9	122	15.6	0.56	15.0	125.9	4.59	119	0.98	2.14	3.5	96.5	11.7	1.7	98.3
5			3.23	41	539	109	0.20	34.5	123	13.4	0.82	12.6	105.8	6.67	119	0.97	2.07	6.0	94.0	11.6	3.0	97.0
6			4.67	41	616	113	0.18	24.8	123	13.9	1.19	12.7	108.3	9.67	117	0.95	2.07	8.5	91.7	11.2	4.1	95.9
7			3.27	42	636	125	0.20	24.5	122	15.5	1.32	14.0	119.7	10.82	117	0.96	2.06	8.4	91.6	11.2	4.2	95.8
8			4.80	42	610	122	0.20	26.5	122	14.9	1.17	13.7	117.2	9.59	117	0.96	1.99	7.6	92.4	11.2	3.9	96.1

* All values except ratios corrected to 1.73 sq. m. of body surface

tensive group, and in the patient with Cushing's syndrome the chloride R/P ratio was less than 1 except during the periods of relative diuresis sipidus show a chloride R/P ratio of less than 1. The chloride U/P ratio tended to be the inverse of the chloride R/P ratio.

4. Relationship Between the Percentage of Filtered Chloride Excreted and the Plasma Chloride Level, the Glomerular Filtration Rate, the Renal Plasma Flow, the Filtration Fraction, and the Chloride Load and the Urinary Flow in Cubic Centimeters per Minute

When the percentage of filtered chloride rejected by the tubules was plotted against each of these factors, no linear relationship was demonstrable.

As can be seen from figure 3 in the two hydrated normal subjects and two hydrated hypertensive patients during the course of a normal "clearance" study, there was no increased tubular rejection of chloride and water by the hypertensive patient as compared with the normal subjects, and likewise there was no relationship between the tubular rejection fraction of chloride and water.

The results obtained when the four additional experiments were performed on the same normal subject (E. C.) serving as his own control, after being primed with desoxycorticosterone acetate, adrenocorticotropic hormone, cortisone and cortisone plus pituitrin, are tabulated in table 2. The following changes were observed:

Normal Subject Primed with Desoxycorticosterone Acetate (DOCA). Figure 4 *A* indicates the minimal effect of desoxycorticosterone acetate. Maximum water diuresis was 2.27 cc. per minute. The maximum per cent of filtered chloride excreted in the urine was 3.7, whereas the maximum per cent of filtered water excreted was 2.1. There is a tendency for chloride to be excreted in excess of water, which is reflected in the relatively low R/P chloride ratio.

Normal Subject Primed with Adrenocorticotropic Hormone (ACTH). The results are shown in figure 4 *B*. The maximum urinary output was 4.1 cc. per minute. The maximum per cent of filtered chloride excreted in the urine was 6.8 with a value of 3.7 per cent for the maximum amount of filtered water excreted. The trend was similar in direction but more pronounced than that obtained with desoxycorticosterone acetate, and the R/P chloride ratio was again low.

Normal Subject Primed with Cortisone. The effect of cortisone was far more pronounced than that of the other two hormones, as shown in figure 1 *C*. The maximum urinary output reached 18.1 cc. per minute. The maximum per cent of filtered water excreted reached 15.6.

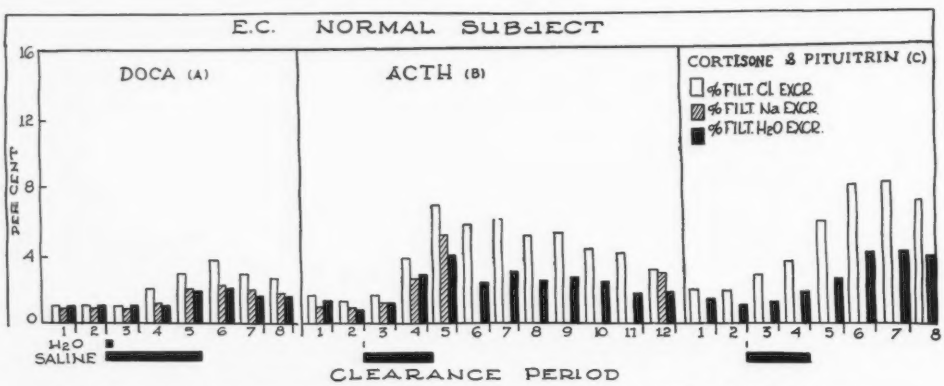

FIG. 4. Comparison of the response of a normal subject primed with DOCA, ACTH, and cortisone and pituitrin administered in the following manner:

DOCA: 5 mg. intramuscularly the day before the experiment; 5 mg. intramuscularly the day of the experiment.

ACTH: 50 mg. intravenously injected after two control periods completed; 50 mg. added to sustaining infusion.

Cortisone and Pituitrin: 200 mg. two days before the experiment; 100 mg. one day before the experiment; 100 mg. the day of the experiment; 0.5 cc. of surgical pituitrin immediately following imbibition of water.

The R/P chloride ratio reached a maximum of 1.09.

Normal Subject Primed with Cortisone, then Given Pituitrin. The results appear in figure 1 *C*. Following the injection of pituitrin the maximum urinary output fell from the control level of 18.1 cc. per minute to 5.27 cc. per minute. There was little change in the maximum percentage of filtered chloride excreted (8.4), but the maximum per cent of filtered water excreted was reduced to 4.2. As a consequence the R/P chloride ratio fell to a maximum value of 0.99. Figure 1 has been grouped to contrast graphically the response of the normal subject with that of the hypertensive patient, and to illustrate the qualitative similarity of the response of the hypertensive patient and the normal subject primed with cortisone.

Discussion

These experiments were initially designed to test the capacity of hypertensive patients to liberate a normal amount of antidiuretic hormone in response to an appropriate stimulus. Impairment of this capacity would indicate impairment of at least one hypothalamic function, and so would lend experimental support to the theory relating hypertension to a disturbance of the hypothalamico-neuro-hypophyseal system.[1-5] The stimulus was the intravenous infusion of a calculated amount of 2.5 per cent saline solution. The response was measured in terms of the subject's ability to inhibit normal diuresis.[6]

If attention be directed to either the detailed tables or the representative graphs, it becomes clear that under the conditions of the experiment, the normal subject is capable of inhibiting diuresis. In contrast, under the same conditions diuresis was not inhibited in either the hypertensive patients or the patient with Cushing's syndrome. This might suggest that in hypertensive patients there is a decreased liberation of antidiuretic hormone and tend to confirm the original hypothesis.

However, when the results obtained on patients with diabetes insipidus are examined, it is obvious that absolute lack of antidiuretic hormone results in a continuous flow of urine that is hypotonic with respect to chloride (fig. 2). This is illustrated by the fact that the U/P chloride ratio remains consistently below 1 (maximum 0.46), whereas the R/P chloride ratio is equally consistently above 1. When the results obtained from the hypertensive patients and the patient with Cushing's syndrome are re-examined (fig. 1 *B* and 2) it is apparent that they fail to show this consistently low U/P chloride ratio, and so have not elaborated a urine which is hypotonic with respect to chloride. Thus, there was no evidence of a relative lack of antidiuretic hormone and no indication of impaired hypothalamic function.

Actually the essential difference between the behavior of normal and hypertensive patients in this procedure is failure of the hypertensive group to retain sodium, chloride and water. This is demonstrated by the fact that the percentage of filtered water, chloride and sodium rejected by the tubules is significantly greater than that rejected by normal subjects (fig. 1 *A* and *B*). Farnsworth[14] also observed an increased tubular rejection of chloride and water in the course of routine clearances performed on hydrated hypertensive patients, and suggested that this increased tubular rejection of water is simply a function of the increased tubular rejection of chloride. This is a tempting explanation, but re-examination of our control periods following 12 hours of dehydration failed to demonstrate an increased rejection of either chloride or water in the hypertensive group. Clearances were then performed on two well-hydrated normal persons and two hypertensive patients (fig. 3). In the presence of a varied urinary output, it was still impossible to demonstrate either increased tubular rejection of chloride and water by the hypertensive patients, or a relationship between the tubular rejection of water and that of chloride; nor was it possible to separate normal subjects from hypertensive patients on this basis. However, under the salt load imposed by the conditions of this experiment, there did seem to be a general relationship between the percentage of filtered water and chloride rejected by the tubules, suggesting that the primary mechanism is failure of the renal tubules to reabsorb the expected fraction of sodium and chloride

offered to them by the glomerular filtrate, and that the hydruria is of secondary importance. Furthermore, these differences are apparently due neither to consistent changes in the electrolyte composition of the plasma nor to changes in renal hemodynamics.

This failure of the hypertensive subject to retain water and salt is unexpected in view of Perera and Blood's[15] demonstration of the tenacity with which these individuals retain salt on a low sodium diet, and the observations of Laramore and Grollman[16] that the muscles of rats with renal hypertension contain increased amounts of sodium and chloride. One explanation might be that the hypertensive patient has a surfeit of tissue sodium and chloride and therefore rejects additional salt more readily. In support of this explanation, it has been pointed out by Peters[17] that in the presence of increased total body water and sodium, hypertonic saline induces diuresis in which salt is excreted in high concentration. Gaudino and Levitt[18] have also indicated that this situation may prevail in hyperadrenocorticism. Further, in Cushing's syndrome desoxycorticosterone paradoxically increases renal excretion of sodium.[19]

Since the results so far did not indicate impaired hypothalamic function and since the results obtained in the hypertensive patient and the patient with Cushing's syndrome were qualitatively similar, our attention was directed to the adrenal cortex and the effect of adrenocorticotropic hormone and certain adrenal cortical steroids on the renal excretion pattern of sodium, chloride and water. It can be seen from figure 4 that the effect of desoxycorticosterone acetate was minimal. The effect of adrenocorticotropic hormone was slightly greater, but, since the maximum effect of adrenocorticotropic hormone is not achieved until eight hours after its intravenous administration,[20] our subject must have been in an intermediate stage of response. The administration of cortisone, however, resulted in profound diuresis (18.1 cc. per minute), and in the elaboration of hypotonic urine with an R/P ratio that was in the high range exhibited by patients with diabetes insipidus.[6] Figure 1 illustrates the similarity of the response of the hypertensive patient and the patient primed with cortisone, as contrasted with the response of the normal subject. It is of interest to note (fig. 4) that when the experiment with cortisone was repeated and pituitrin administered, the urinary output was greatly reduced, but the excretion of chloride was unchanged. This is reflected by the extremely low R/P ratio. As also observed by Lauson,[21] no chloruretic effect of pituitrin could be demonstrated.

From these studies no specific conclusion can be drawn. It can be stated, however, that of those hormones tested under the conditions of this experiment, response to cortisone most nearly approximates the response of hypertensive patients. The difference between the two is primarily a difference between the relative proportion of water and electrolytes excreted in the urine, a difference which can be overcome by the simultaneous administration of pituitrin.

Summary and Conclusions

1. A modification of the technic of Hickey and Hare was applied to a series of normotensive individuals, to patients with essential hypertension, Cushing's syndrome and diabetes insipidus and to a normal subject primed with desoxycorticosterone acetate, adrenocorticotropic hormone, cortisone and cortisone and pituitrin with the following results: (*a*) In normotensive subjects the intravenous infusion of hypertonic saline inhibited water diuresis. (*b*) In hypertensive individuals with or without Cushing's syndrome water diuresis was not inhibited and the renal tubules rejected an abnormally large fraction of filtered sodium and chloride. (*c*) Subjects with diabetes insipidus failed to exhibit antidiuresis but their renal tubules continued to reabsorb a normal fraction of filtered sodium and chloride.

2. Under reasonably basal conditions the normotensive and hypertensive individuals could not be distinguished on the basis of the relation of reabsorbed to filtered sodium and chloride. The difference appeared only under the stress imposed by an increased load of hypertonic saline.

3. These results suggest that hypertension with or without Cushing's syndrome is not

accompanied by hypopitressinemia, since the tubular rejection of filtered sodium and chloride greatly exceeded that of the patients with diabetes insipidus.

4. There was a striking similarity between the response of the patient with hypertension and the normal subject primed with cortisone.

5. Pituitrin neutralizes the diuretic response to cortisone but has no effect on the reabsorption of sodium and chloride.

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Sumario Español

Hace tiempo que ha habido interés en la posibilidad de que una relacción existe entre la hipertensión esencial y las aberraciones endocrinas que envuelven el hipotálamo, la pituitaria y la corteza adrenal. Este trabajo representa un atentado para estudiar estas relacciones indirectamente por medio de un examén de la manera en que los rinones de pacientes con estas enfermedades manejan el agua, el sodio y los cloruros.

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Ballistocardiography

An Appraisal of Technic, Physiologic Principles, and Clinical Value

By RICHARD S. GUBNER M.D., MANUEL RODSTEIN M.D., AND HARRY E. UNGERLEIDER M.D.

THE various modalities used in the study of the heart and circulation contribute different types of information. Some, such as electrocardiography and fluoroscopic or roentgenographic study, have such broad spheres of usefulness that they are almost routinely employed. Other diagnostic procedures have not gained wide usage either because of expense of equipment, difficulty in clinical application, specialized nature and limited value of information provided, or because such information as is provided unnecessarily duplicates what may be learned in simpler fashion. It is the object of this survey to appraise the clinical usefulness of ballistocardiography, a technic which records the movements imparted to the body by the forces associated with contraction of the heart, and acceleration and deceleration of blood as it is ejected and moved in the large vessels. Parenthetically it may be remarked that the ballistocardiogram provides, in simple and routinely applicable fashion, a considerable body of useful information not otherwise obtainable; and hence fulfills the criteria of a valuable adjunct in examination of the heart.

I. PHYSICAL PRINCIPLES AND TECHNICS OF RECORDINGS

The principle of ballistocardiography is Newton's third law of motion, namely, for every acting force, there is an equal and opposite reacting force. Hitherto a euphemistic term, the expression "force of the heart" has become meaningful and measurable by ballistocardiography. Although clinical interest dates from Starr's important contributions,[1] ballistocardiography has a fairly venerable history which has been reviewed elsewhere.[2-4] A regular and reproducible procession of waves is recorded in the ballistocardiogram, the major components of which have been designated by Starr[1] as the H, I, J, K, L waves. These waves are clearly associated with specific events in the cardiac cycle, but their precise qualitative, let alone quantitative, interpretation has been far from definitive for several reasons.

Both sides of the heart contribute to the ballistocardiogram in significant and continually varying degree so that it is difficult to dissociate the relative effects of right and left ventricular activity. The waves recorded are in no sense pure forces but the resultant vectors of variously and, in part, oppositely directed forces. When the heart rate is rapid, superimposition of waves reflecting forces associated with events in diastole occurs on early systolic waves of the following cycle. In consequence it becomes difficult or impossible to interpret the ballistocardiogram when tachycardia is present. Most of the ballistocardiographic technics presently employed record only those forces exerted in the longitudinal axis of the body, which best portray the major forces associated with cardiac contraction.

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However, the dominant vectors associated with certain aspects of blood flow in the cardiac cycle may be exerted in other directions, and to this end ballistocardiograms may be recorded in other planes such as the lateral direction[5] or multispatial vector registration.[6-9]

The forces generated by expulsion of blood from the heart and propulsion in the great vessels must be transmitted through the tissues, skeleton and panniculus to the recording system. Accordingly, the compliance of the body structures, in addition to the natural period of motion of the body (which falls within the frequency spectrum of ballistocardiographic waves), impose some modifications on the waves. Needless to say body motion, such as muscular activity, must be minimized during recording. Ballistocardiograms therefore are unsatisfactory unless the subject is completely relaxed, a circumstance which makes ballistocardiography difficult in the upright position, and in aged and ill subjects, who find it difficult to lie in the recumbent position on a hard unyielding surface.

Ballistocardiographs with which most experience has been gained have employed a suspended table on which the subject lies; body movements are translated into longitudinal movements of the table, which are recorded. Multiple and important distortions are produced in the ballistocardiographic waves by the natural frequency characteristics of the recording table, as has been pointed out by Rappaport.[10] The high frequency undamped table developed by Starr possesses a natural frequency of approximately 9 cycles per second. With the Starr table low frequency waves are damped and do not register with the same amplitude as higher frequency waves of the same magnitude. In one respect this confers an advantage for the very low frequency respiratory waves (approximately ⅓ cycle per second) are eliminated; if recorded they cause a wavy baseline in the ballistocardiogram and make analysis difficult. However the lower frequency waves of the cardiac cycle itself up to several cycles per second are damped so that there is a distortion in magnitude varying with the cycle frequency of the waves. In addition to the distortion in magnitude produced by the frequency response slope which affects the low frequency waves, another form of distortion which is termed differentiation is produced by introduction of the time constant. A spurious negative wave follows a steeply sloped positive wave. This causes an artefact in the K wave, the negative wave following the steep J wave upstroke, and introduces an error of real clinical significance in circumstances where the K wave is of interest, such as coarctation of the aorta, presently to be mentioned. Still another error in the Starr table is that of phase shift, whereby there is a time lag in deflection after the applied force.

To obviate the distortion inherent in the Starr table, Nickerson[11] introduced a low frequency (1.5 cycles per second) critically damped table. Since low frequencies are recorded with Nickerson's method, respiratory movements are imposed on the ballistocardiographic tracing causing a wavy baseline which may make interpretation of the record difficult unless respiration is suspended. The validity of ballistocardiograms obtained with Nickerson's modification has been questioned.[10] Although the frequency response differs from that in the Starr table it is not flat over the range of ballistocardiographic waves but exhibits a drooping slope, resulting in three important types of distortion, that is, reduced amplitude of the waves, increased duration of the complexes and temporal phase displacement.

Apart from the cumbersomeness and general unavailability of the Starr and Nickerson tables, it is apparent that the interposition of the table in the recording of the ballistocardiogram introduces significant distortion. Accordingly, considerable interest has attended the introduction of more direct and much simpler methods for inscribing ballistocardiograms. It is not possible to comment individually on all the numerous ingenious recording devices, which have ranged from the bathroom scale to the seismograph in complexity. The simplest and cheapest types of apparatus, which, properly constructed, exhibit least inherent distortion characteristics, are the electromagnetic and photoelectric instruments introduced by Dock and Taubman.[12]

The actual recording of the ballistocardiogram with these technics is carried out on the electrocardiograph. With both these methods, as well as a variety of modifications which have been introduced, a bar is placed across the shins with the subject lying recumbent on a rigid table or on the floor. The bar moves in unison with the body and its movements are translated into electrical potential.

The physical principles of the photoelectric instrument and electromagnetic instrument are quite different. The photoelectric type records displacement, the electromagnetic type records velocity of body motion, that is, the rate of body displacement. While the two are broadly parallel they are not synonymous, and velocity changes may precede displacement by several hundreths of a second. This is of some importance in interpreting the physiologic origin of the ballistocardiographic waves in relation to other simultaneously recorded events in the cardiac cycle. Although a pure velocity curve is theoretically desirable in registering the forces associated with cardiac ejection and blood flow it is not practicable. Unless the subject is exceptionally well relaxed artefacts are introduced with the least body motion. Recently Smith and Bryan[13] have described a low frequency electromagnetic velocity measurement ballistocardiograph with filter circuits to eliminate body tremor components.

Voltages induced by movement of a wire coil in an electromagnetic field exhibit a steep rising response with increasing frequency in the frequency range of ballistocardiographic waves. Accordingly high frequency waves are selectively amplified much more than low frequency waves, as obtains also in the Starr table. In addition, other forms of distortion, namely, differentiation (artificial K wave) and temporal phase displacement are present as seen also on the Starr table. With the photoelectric instrument the frequency response is flat so there is no differential amplification of waves with varying frequency, and distortion due to differentiation and temporal phase displacements are likewise eliminated.[10] Because of the difficulty in achieving a pure velocity curve, undistorted and free from artefact, in the electromagnetic ballistocardiograph, condensers varying from 20 to 70 microfarads have been introduced across the coils. The condensers have the effect of modifying the frequency response curve to make it substantially flat between 1 and 10 cycles per second, in the range of the ballistocardiographic waves. Appreciable damping is still present below 1 cycle per second which has the virtue of eliminating the very low frequency respiratory movement, although respiratory movement is still evident when a 70 microfarad condenser is employed. For routine purposes a 20 or 50 microfarad condenser is thoroughly satisfactory, and the records obtained are in effect displacement curves similar in every respect to the photoelectric curve, and relatively free of the forms of distortion mentioned. The change in the ballistocardiogram from velocity to displacement type of curve as condenser capacity is increased in the electromagnetic instrument is shown in figure 1.

Because of their simplicity, relative accuracy, and inexpensiveness, the electromagnetic and photoelectric types of ballistocardiograph appear to be the best suited for routine use as a convenient portable accessory to the electrocardiograph.

It is desirable that the amplitude of the recorded waves be sufficiently large to permit detailed inspection of their individual components. With the electromagnetic instrument amplitude is much greater with the 20 microfarad condenser than with the 50 or 70 microfarad condenser. Unless a very sensitive photo cell is employed the amplitude of waves in the photoelectric instrument may be too small to allow satisfactory interpretation. Individual instruments should be standardized by adjusting the sensitivity of the recording arm of the electrocardiograph so that in normal young adults the amplitude of the maximum ballistocardiographic deflection is between 2 and 3 cm. In this manner if appreciable reduction in wave amplitude is present in abnormal situations it will readily be apparent. If quantitive standardization is desired (which in clinical practice is of little importance) the shoulder may be struck with a 200,000 dyne blow delivered by a pendulum, which, with sensitivity of the electrocardio-

graph set at 1 cm. deflection per millivolt, will give a deflection of 8 to 10 mm. in subjects weighing 70 Kg.[12] With standardization it is possible to calculate the maximum force developed during ventricular ejection. Employing calibration of 280 Gm. to displace the recording beam 1.0 cm., Starr found the vertical amplitude from the I depth to the J peak to provide an estimate of the maximal force delivered in systole, that is, a measurement of cardiac strength.[14]

One further technical feature of ballistocardiography warrants mention. When ballistocardiographic patterns are abnormal it is difficult or impossible to identify the individual waves properly unless simultaneous registration is made of another event in the cardiac cycle, such as the electrocardiogram, heart sounds or arterial pulse, enabling orientation to known phases of the cardiac cycle. Multichannel instruments are not generally available but fortunately the electrocardiogram may be surmounted on the ballistocardiogram by attaching an electrocardiograph lead (such as lead I) in series or parallel circuit with the ballistocardiogram. In this manner a QRS spike will be recorded just before the ballistocardiographic waves associated with systolic contraction, permitting identification of the waves. Methods have been described to enable selective tuning of the electrocardiogram in or out of the ballistocardiograph circuit, so that the amplitude of the QRS complex may be varied as desired.[15-17]

II. Origin and Physiologic Significance of the Waves

H Wave (Presphygmic Wave). The first wave associated with contraction of the heart is an upward deflection, the H wave, which normally is relatively small and inconspicuous; in heart disease, as will presently be mentioned, it may become large in amplitude equalling or surpassing the height of the J wave. Study of the H wave with the velocity type ballistocardiograph (2 microfarad electromagnetic instrument), which possesses least time lag, together with simultaneous electrocardiogram and heart sounds recorded at high speed (75 mm. per second), indicates the following time relationships (fig. 1). The H wave begins .02 to .03 second, or even earlier, after the onset of electrical activation of the ventricles (onset of QRS complex), and .02 to .03 second before

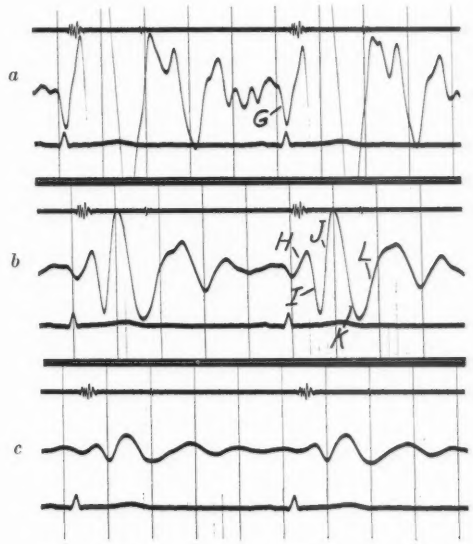

Fig. 1. Electromagnetic ballistocardiograms recorded with, (*a*) 2 microfarad condenser (velocity tracing), (*b*) 20 microfarad condenser (chiefly displacement), and (*c*) 70 microfarad condenser (displacement tracing). Amplitude of the waves decreases as condenser capacity is increased. In the velocity tracing (*a*), the J and K deflections are too rapid and large to be defined clearly in reproduction. A time lag is also introduced by the condensers. With the velocity tracing the onset of the H wave occurs 0.025 second after beginning of QRS complex, in the displacement tracing this interval is 0.04 to 0.05 second. Peak of H is attained in 0.10 second after onset of QRS in velocity tracing, in 0.13 second after onset of QRS in displacement tracing. Velocity tracings give a truer temporal record of ballistocardiographic waves in relation to other events of the cardiac cycle. The H wave commences 0.02 to 0.03 second before the first component of the first heart sound and is the earliest mechanical event in systole. With the velocity tracing a distinct downward wave, the G wave, is seen to precede the H wave. This begins before the onset of the QRS complex and is associated with auricular systole.

the first component of the first heart sound. Its duration varies from .05 to .07 second, and the wave terminates almost simultaneously with the end of the first heart sound. The

termination of the relatively slow H upstroke is marked by the onset of a steep downstroke, the I wave, which is associated with ventricular ejection.

Various interpretations have been offered for the H wave. It has been suggested that the H wave is due to auricular contraction,[18] but this cannot be so since H waves are observed in the presence of auricular fibrillation. There is frequently observed a distinct downward wave preceding the H wave which evidently is associated with auricular systole, and which follows the P wave and precedes the QRS complex (fig. 1). This has been termed the G wave and may be quite distinct when the heart rate is slow. The auricular components of the ballistocardiogram may be seen more distinctly in heart block where auricular and ventricular contraction are more clearly dissociated. Another explanation which has been advanced for the H wave is that it is due to the apex thrust of the heart.[19] A clear indication that this cannot be the case is afforded by ballistocardiograms in subjects with extrasystoles. The beat following the compensatory pause after the extrasystole is more forceful than succeeding regular beats and the apex thrust is greatest, yet the H wave is smaller in beats following extrasystoles than in subsequent regular beats. Furthermore, were the H wave related to apex thrust one would not expect it to be amplified in heart disease, which occurs very frequently.

An explanation for the H wave which appears to be most valid is that it reflects forces associated with abrupt deceleration in the flow of blood returning to the heart. With the sudden rise of intraventricular pressure accompanying the onset of systole, blood flow into the ventricles is abruptly halted and this sudden deceleration is reflected in the H wave. This circumstance occurs even before the closing snap of the auriculoventricular valves which produces the first heart sound, and accordingly, where the H wave is distinct, a sensitive index is produced of the initial event in ventricular systole, that is, a rise in intraventricular pressure. Since the beginning of the succeeding I wave marks the onset of ejection, the duration of the H wave reflects the duration of the isometric or presphygmic period of ventricular contraction. The values observed, .05 to .07 second, accord well with measurements obtained by catheterization and other less direct technics.

I and J waves (*Ventricular Ejection*). The onset of ejection is marked by a sharp negative wave, the I wave, which represents the footward recoil of the body from acceleration of blood upwards in the pulmonary artery and ascending arch of the aorta. With impact on the crown of the two arches, the direction of forces is abruptly reversed and there is a sharp recoil of the body in the headward direction, the J wave. Accessory factors in the production of the J wave are acceleration of blood flow in the descending aorta and deceleration of flow leaving the ventricles and in the ascending arches.

The J wave normally is the dominant wave of the ballistocardiogram; its amplitude is two to three times that of the I wave. In form, both I and J waves are steep, unbroken and attain pointed summits. The peak of the J wave normally occurs between 0.22 and 0.26 second after the onset of the QRS complex of the electrocardiogram. In abnormal situations the I and J are decreased in amplitude, the I wave may not be evident, the J wave becomes slurred and notched and its peak is delayed to 0.28 second or even longer after the onset of the QRS.[20]

The I and J waves are clearly related to ventricular ejection; indeed, much of the ballistocardiographic literature has been devoted to attempts to calculate the cardiac output from the amplitude and areas of the IJ stroke. Although a fair correlation exits,[1, 11, 21-23] the amplitude of the I and J waves is more directly related to the velocity than to the quantity of ejection. The velocity and quantity of ejection ordinarily correlate closely but this relationship does not necessarily obtain. In shock the stroke output is markedly decreased but ejection velocity is increased.[24] Under such circumstances cardiac output calculated by methods predicated on ejection velocity, such as the ballistocardiograph,[25] or pulse contour,[26] give values far in excess of the actual output determined by the

Fick procedure. Conversely when ejection velocity is reduced, as in heart failure, values for output obtained by these methods are too low.[27]

Studies of instantaneous arterial blood flow with the electromagnetic flowmeter[28] indicate that maximum velocity is normally attained early in systole, at a time coincident with the I and J ballistocardiographic deflections. The form and amplitude of the I and J strokes may be quantitatively integrated with the instantaneous components of ejection, that is, the form of the cardiac ejection curve.[14] Abnormalities in form and decreased amplitude of the I and J strokes accordingly signify a reduced velocity and force of ejection. As indicated by Starr and his coworkers[14] the ballistocardiogram is more closely related to the heart's force than to its output, and the vertical amplitude between the trough of the I and peak of the J provides an accurate index of the maximal force developed by the heart in individual systoles in giving acceleration to the flow of blood.

One of the most striking characteristics of the I and J ejection strokes is the phasic variation in amplitude with respiration. With the onset of inspiration the waves augment in amplitude, and conversely they decrease during expiration. In normal young subjects during ordinary shallow respiration the variation of amplitude is of modest degree. It is more conspicuous during deeper breathing, and in normal shallow breathing in older subjects and in those with heart disease (fig. 2).

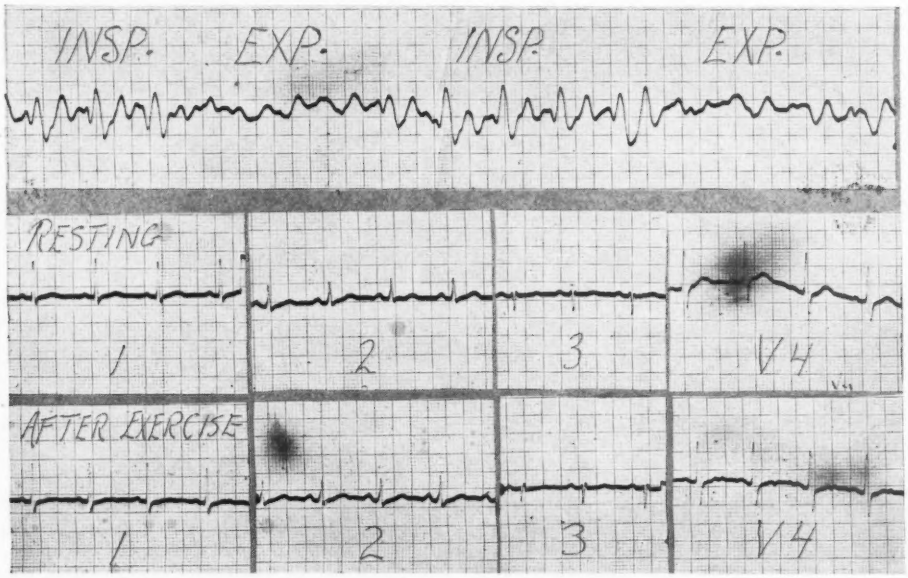

FIG. 2. Respiratory variation in male, age 41, with anginal syndrome. During expiration, which best reflects left ventricular activity, the identity of the waves is completely lost, in inspiration the complexes are of normal configuration. Electrocardiogram at rest (middle strip) is normal. Tracing after exercise (lower strip) shows evidence of coronary insufficiency, indicated by flattening of T wave in lead I, and semi-inversion of T wave in lead V_4.

Although the left ventricle is much more powerful than the right ventricle, a considerable proportion of the work of the left ventricle is expended in overcoming the arterial pressure, and this is not reflected in the IJ wave of the ballistocardiogram. There is much less disparity between the two ventricles in the forces expended in accelerating the flow of blood, which is the determinant of the I and J strokes. Consequently the left and right ventricles contribute to the I and J waves in almost equal measure, as injection experiments in cadavers have shown.[14]

The respiratory variation in the ballistocardiographic waves is due principally to the profound influence of respiration on right ventricular filling and ejection. Ordinary respiration has much less influence on left ventricular output. The negative intrathoracic pressure accompanying inspiration sucks venous blood into the right cardiac chambers so that right ventricular output is increased 25 per cent or more. Left ventricular output varies in the inverse direction but only negligibly, so that left ventricular ejection is relatively constant (a circumstance important to circulatory efficiency), while right ventricular ejection undergoes wide swings during respiration.[29, 30] The lungs serve as a buffer to equilibrate flow to the left ventricle, and during inspiration there is an increase in the volume of blood contained in the pulmonary vessels. Acceleration of this augmented quantity of blood in the pulmonary vessels during right ventricular systole, as well as altered velocity of flow in the pulmonary vessels during inspiration may be auxiliary factors in accounting for the increased IJ stroke in inspiration, in addition to increased right ventricular output. A further factor which may contribute to an augmented J amplitude in inspiration is the greater percentage of pulmonary blood flow which is directed in the footward direction with descent of the lungs and diaphragm during inspiration. An analogous effect is readily demonstrated in systemic arterial flow by recording ballistocardiograms with the arms extended above the head in the

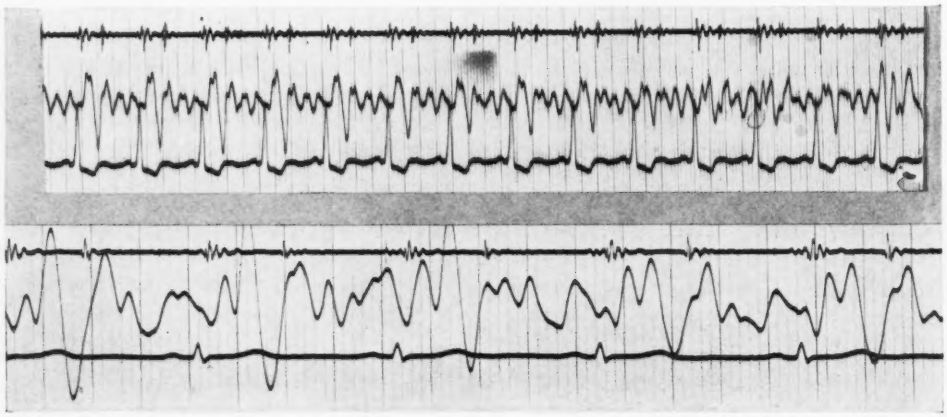

FIG. 3. Deep K wave. Top strip is of subject with hypertensive heart disease. In addition to the abnormally deep and early K wave, the I wave is absent and J wave is notched. Bottom strip (high speed recording) illustrates deep K wave in subject, age 65, with arteriosclerosis of aorta and hypertension. The trough of the K wave is early (as also in the top strip) and is attained 0.05 to 0.06 second before the first component of the second heart sound. Normally the K trough occurs 0.01 to 0.02 second before the second heart sound. Exaggerated and early K waves are associated with inelasticity of the aorta. The depth of the K wave is also related to the length of the aorta. Deep K waves are seen normally in tall individuals. Note considerable respiratory variation in J wave amplitude in these two abnormal individuals.

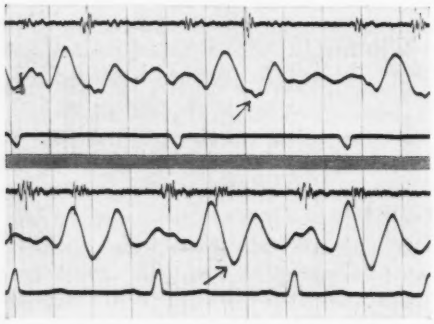

FIG. 4. Coarctation of aorta. The top strip, from a male, age 30, with blood pressure 186/100, shows marked blunting of the K wave. Lower tracing, made postoperatively after surgical correction of coarctation of aorta shows normal K waves.,

axis of the body and then in their normal position. The J stroke decreases as the arms are extended cephalad and increases when placed at the sides of the body.

A convincing demonstration that the intrathoracic pressure variations, with accompanying changes in right ventricular output, are the major factors in respiratory variation in the ballistocardiogram has been provided by Starr and Friedland[31] who demonstrated that when the intrathoracic pressure relationships during respiration were reversed by positive pressure inspiration and passive expiratory deflation, the ballistocardiographic respiratory variation was similarly reversed in phase.

The K Wave (Aortic Deceleration). The K wave, as has already been indicated, is profoundly influenced by the type of recording instrument. It is recorded with some measure of fidelity only with the displacement type of apparatus. The K is a footward wave commencing at the peak of the J and extending in an unbroken, relatively steep slope to a deep trough at a level approximating or slightly beyond the depth of the I wave. The trough of the K wave normally precedes the onset of the second heart sound by 0.01 to 0.02 second.

The K wave, unlike the I and J waves, is due entirely to the systemic circulation. Its trough is coincident with the peak of the femoral

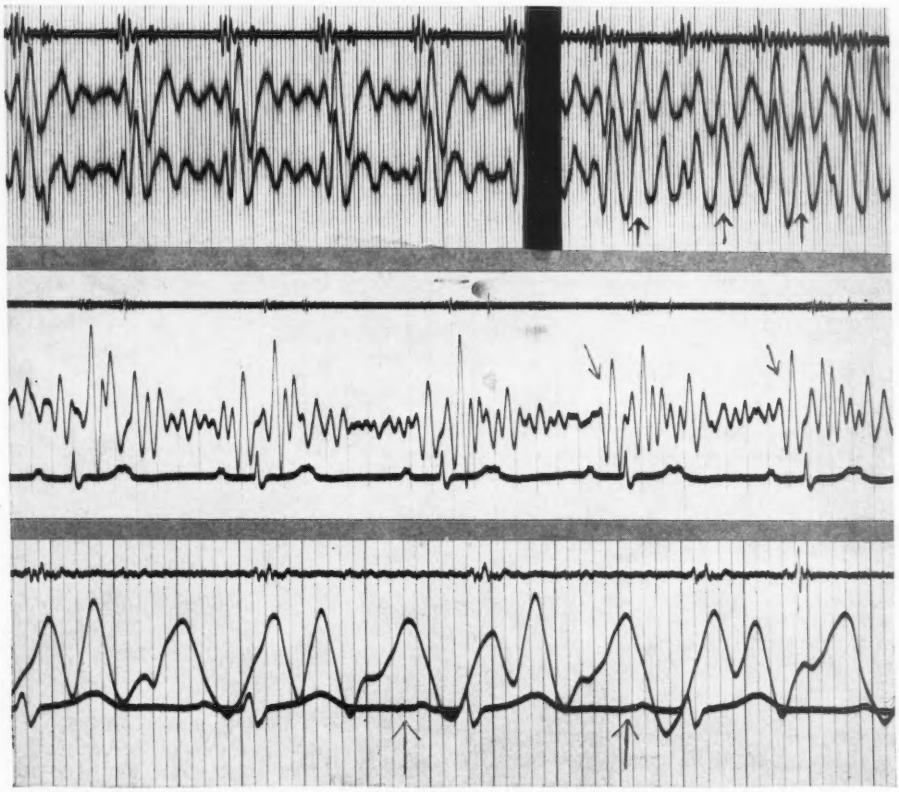

FIG. 5. Large diastolic waves. Top strip shows normal individual at rest and during Valsalva experiment. Second part of strip, during Valsalva procedure, exhibits greatly augmented L wave, associated with obstruction to return flow to heart. Middle strip in subject with 2:1 heart block reveals large waves following auricular systole (P wave) independent of ventricular activity. In some beats (latter two) the diastolic auricular ballistocardiographic waves exceed those accompanying ventricular systole. Lower strip, in subject with subclavian arteriovenous aneurysm, reveals large diastolic wave.

pulse curve.[32] It is caused by deceleration of blood flow in the descending aorta as it is slowed by the peripheral resistance and as ejection velocity falls off at the end of systole. When peripheral resistance is decreased by producing reactive hyperemia of the lower extremities the K wave decreases in amplitude.[18] Conversely the K wave is increased in amplitude and attains an earlier trough with increased peripheral resistance and arterial

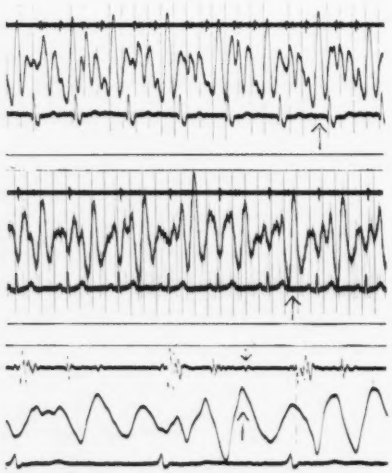

FIG. 6. Large diastolic waves in rheumatic mitral valvular disease. Top strip, from subject with advanced mitral stenosis and insufficiency and markedly enlarged heart, reveals major wave amplitudes to be diastolic in time. Middle strip, from subject with mitral insufficiency, shows L wave greatly exceeding J in amplitude. Lower strip (high speed recording), from subject with mitral stenosis, similarly shows large amplitude L wave, whose peak coincides with protodiastolic gallop sound. Unless simultaneously recorded with heart sounds or electrocardiogram the ballistocardiographic waves of these subjects could not be identified.

inelasticity as in hypertension, and arteriosclerosis of the aorta associated with aging (fig. 3). The depth of the K wave is directly related to the length of the descending aorta. When the length of the descending aorta is greatly shortened, as in model experiments and clinically in coarctation of the aorta,[19, 33, 34] the amount of blood in the descending aorta undergoing abrupt deceleration is greatly reduced and the K wave may disappear (fig. 4). This is a useful diagnostic sign in intraluminal obstruction of the descending aorta.[35, 36]

L Wave, and Diastolic Waves (M, and others). Originally considered as resulting from body after vibrations, the L wave and subsequent waves in diastole are now recognized to be associated with circulatory forces. The L wave is a relatively slow wave representing headward thrust which begins at the trough of the K wave. It is of variable form and amplitude, reaching a plateau rather than a sharp peak at a height considerably below the peak of the J wave. The L and subsequent diastolic waves in the ballistocardiogram are considered by Hamilton[19] to represent forces in the aorta. These waves are of complex origin and cannot be ascribed to any single phenomenon of blood flow. In some measure, at least, these waves must be associated with return flow to, and filling of, the heart; for in abnormal situations such as gallop rhythm, mitral valvular disease, constrictive pericarditis, myocarditis, heart failure, the Valsalva experiment, and arteriovenous aneurysm the L wave and subsequent waves may be of great amplitude and even exceed the IJ wave of ventricular ejection (figs. 5 and 6).

III. Clinical Interpretation of the Ballistocardiogram

If the ballistocardiogram is to attain status as a clinical instrument in the diagnosis of heart disease some criteria for interpretation are necessary. It is desirable to relate such criteria and terminology, so far as is possible, to specific circulatory phenomena.

Certainly any scheme of interpreting the ballistocardiogram must take account of respiratory variation, exaggeration of which is the commonest abnormality encountered in heart disease. It has already been indicated that respiratory variation in the ballistocardiogram is due to phasic changes in right ventricular filling and ejection. At first glance it seems paradoxic that respiratory variation, which is primarily due to right ventricular changes, should be so conspicuous in types of heart disease such as coronary disease which principally involve the left ventricle. Although the right and left ventricles contribute to the formation of the I and J waves in almost equal

degree, the right ventricular component is much larger in inspiration, the left greater in expiration.

The levo and dextro ballistocardiogram components of the IJ wave may be separated in large measure by a modified Valsalva maneuver. If a subject exhales, after a deep inspiration, against a resistance of 25 cm. water, the marked increase in intrathoracic pressure abruptly halts filling and emptying of the right ventricle, while left ventricular ejection is actually augmented for a few beats until the pulmonary vascular bed is drained. Consequently at the beginning of expiration against pressure a levo ballistocardiogram is obtained, that is, the IJ stroke represents almost pure left ventricular ejection. In normal individuals the normal form of the I and J waves is maintained though amplitude is reduced, in subjects with heart disease the complexes become greatly reduced in amplitude and abnormal in form. With the sudden fall in intrathoracic pressure on termination of this maneuver and the succeeding inspiration, the right ventricle is filled and its ejection is large, while left ventricular ejection is still small. At this point a dextro ballistocardiogram is recorded.

In effect, to a less complete degree than obtained in the Valsalva procedure, the ballistocardiogram during inspiration is a dextro ballistocardiogram and during expiration it is a levo ballistocardiogram. Abnormalities in the force of left ventricular ejection are masked during inspiration and become revealed only in expiration when right ventricular ejection is reduced. These circumstances appear to explain adequately the reason for the exaggerated respiratory variation in heart disease involving the left ventricle (figs. 2, 3, 7, 8). When the I and J waves are grossly abnormal both in inspiration and expiration it

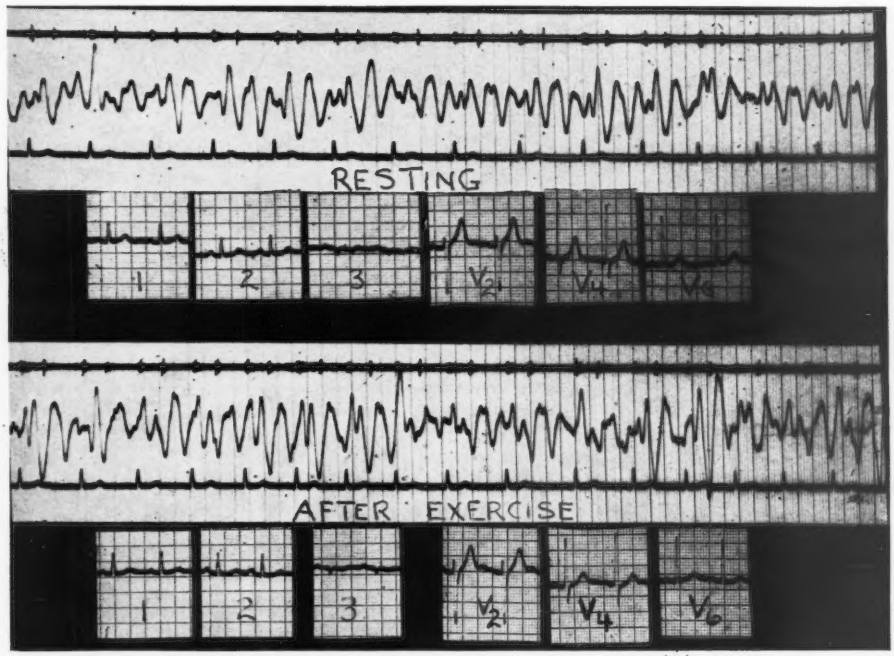

FIG. 7. Ballistocardiographic changes following exercise in male, age 46, with previous posterior wall infarct. The ballistocardiogram, markedly abnormal at rest (note phasic variation in IJ waves), became abnormal five minutes after exercise (thirty 18 inch ascents in two minutes) to such a degree that no identification of the waves is possible. The electrocardiogram, normal at rest showed no significant changes in serial tracings after exercise. This illustrates that there is no necessary correlation between the electrocardiogram and ballistocardiogram in coronary disease.

must be assumed that there is a general impairment in the force of cardiac ejection involving the right as well as the left ventricle.

Inasmuch as the Valsalva maneuver appears to afford a better dissociation than normal respiration (which varies in depth in different subjects) a modified Valsalva test may be employed in ballistocardiography to provide an index of the force of the right and left ventricular ejection individually. If subjects exhale through a tube whose orifice is placed in water at a depth of 15 to 25 cm., a steady exhalation may be carried out without undue straining and without distortion of the ballistocardiogram by somatic tremor.

In interpretation of the ballistocardiogram, to recapitulate, the first and most important aspect to be studied and described is the force of ventricular ejection, and more specifically right and left ventricular ejection individually as indicated by the IJ wave in inspiration (right ventricle), and in expiration (left ventricle), during continuous breathing. Such information may be provided more adequately by a modified Valsalva procedure. As has already been mentioned the form and time relationships of the J wave are important as well as its amplitude. When ejection velocity and force are impaired, abnormality of the ventricular component of the ballistic complexes is revealed not only by decreased amplitude of the IJ stroke, but by disappearance of the I wave, slurring and notching of the J wave, and delayed attainment of the J peak.

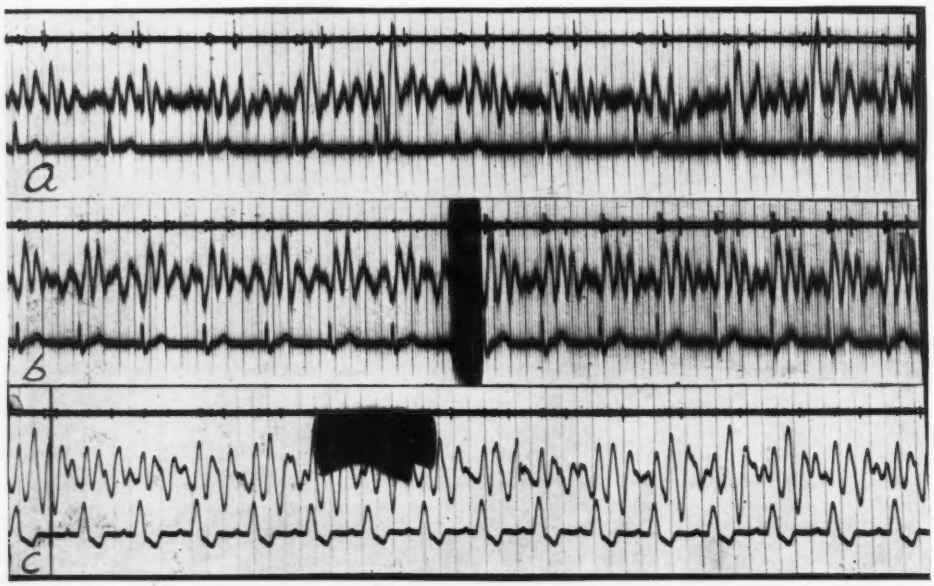

FIG. 8. Ballistocardiograms of three subjects with arteriosclerotic heart disease: (*a*) male age 62, (*b*) male age 61, (*c*) male age 57. Respiratory variation is marked in records *a* and *c*. H wave is of large amplitude in *a*, *b*, and *c*. I wave is phasically poor in records *a* and *c*, and in record *b* made with respiration suspended first in inspiration then in expiration. J wave is delayed in records *a*, *b* and *c*. The peak of J is attained 0.28 second after onset of QRS in *a* and *b* and 0.30 second after onset of QRS in *c* where left bundle branch block is present. J is phasically slurred, notched and of low amplitude in record *c*.

A simplified scheme of grading the ballistocardiogram has been employed by Brown, Hoffman and de Lalla,[37] which places primary emphasis on respiratory variation. Four grades of abnormality are scored:

Grade 1—Regularity of complexes is preserved. Amplitude in inspiration is normal, in

expiration amplitude is decreased and varies in definitiveness.

Grade 2—One half or more of the complexes are abnormal, mainly in expiration. The inspiratory amplitude is decreased somewhat also.

Grade 3—Abnormalities are present in inspiration as well as expiration, but the complexes are still identifiable.

Grade 4—All the waves are unidentifiable and of low amplitude.

The second factor in the ballistocardiogram which should be inspected and described after noting the IJ wave and respiratory variation is the K wave, the wave of aortic deceleration. It should be observed whether the K wave is unusually shallow or deep, and the timing of its trough, either in relation to the second heart sound, or if heart sounds are not recorded, the time interval from the onset of ventricular ejection (peak of H wave) should be studied. As has already been mentioned the K wave is shallow or absent in coarctation of the aorta, and it is accentuated and attains an early trough in hypertension and arteriosclerosis (figs. 3 and 4).

The third factor in analysis of the ballistocardiogram pertains to waves associated with return flow, the L waves, and subsequent diastolic waves. The H wave falls into this category, for although related to the onset of ventricular systole (presphygmic period) it is due to the abrupt deceleration of blood flow returning to the heart. Abnormally large H, L and diastolic waves are frequently observed in heart disease and may at times be the only abnormality present (figs. 5 and 6).

In summary, then, interpretation of the ballistocardiogram may be conveniently subdivided into three aspects: (1) force of left and right ventricular ejection (IJ wave), (2) aortic wave (the K wave), and (3) waves of return flow (H, L and diastolic waves).

Abnormalities in Ejection

Clinical interest in ballistocardiography has focussed particularly on investigation of its usefulness in coronary artery disease. The succinct observations of Starr and Wood,[38] who were the first to study this problem extensively, will not be repeated but will merit rereading.

Numerous studies have confirmed and extended the observations of Starr and Wood.[16, 37-57] Notwithstanding the varying technics employed and the absence of uniform criteria of interpretation, there has been a surprising unanimity in the ballistocardiographic findings in coronary disease among different investigators. These may be summarized briefly as follows:

In acute myocardial infarction, the ballistocardiogram is quite regularly abnormal. During recovery, the ballistocardiogram tends to improve, particularly in younger subjects in whom it often reverts to normal form. Normal ballistocardiograms following coronary occlusion are helpful in indicating restoration of functional integrity of the contractile mechanism of the myocardium. In angina pectoris and in asymptomatic coronary artery disease likewise, the ballistocardiogram is almost invariably abnormal. Subjects with normal resting electrocardiograms who manifest electrocardiographic evidence of coronary insufficiency following exercise or anoxemia commonly exhibit abnormal ballistocardiograms at rest. Following exercise or anoxemia or meals in such individuals, the ballistocardiogram tends to become increasingly abnormal.

Inevitably, despite Starr and Wood's injunction that the ballistocardiogram and electrocardiogram measure different activities of the heart, comparisons have been drawn of their relative value in the diagnosis of coronary disease. There seems little doubt that abnormalities occur more commonly in the ballistocardiogram than in the electrocardiogram, both at rest and after stress (fig. 7). The sensitivity of the ballistocardiogram, however, imposes very serious limitations on its practical diagnostic value. Ballistocardiographic patterns encountered in coronary artery disease are illustrated in figures 2 and 8.

The Effect of Aging. Several studies on large groups of presumably normal individuals have uniformly shown a rapid increase of abnormal ballistocardiographic patterns with advancing age.[20, 40, 41, 43-45, 49] Employing Brown's grade 2

or over as indicative of significant abnormality, Franco[44] found over 50 per cent of ballistocardiograms abnormal among 317 normal individuals without any evidence of cardiovascular disease, whose ages ranged from 35 to 64. Above the age of 45 over one-third of male subjects exhibited abnormal patterns, and above the age of 60 years tracings were abnormal in the majority of cases.

Starr and Hildreth[58] have itemized the changes in the individual waves with aging.

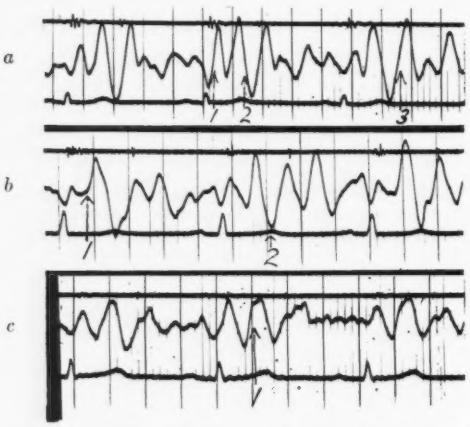

FIG. 9. Ballistocardiograms in three older normal subjects, exhibiting various abnormalities.

(*a*) age 58. 1. Large H wave. 2. Deep K wave. 3. Large L wave.

(*b*) age 56. 1. Absent I wave. 2. Early K wave.

(*c*) age 65. 1. Slurred, low amplitude J wave.

Their data provide useful empiric normal standards for the amplitudes and ratios of the individual waves of ballistocardiograms recorded by high frequency instruments. Standards for the low frequency, critically damped displacement ballistocardiograph have been presented by Jones,[16] and for low frequency velocity ballistocardiograms by Smith and Bryan.[13] In successive decades from age 20 to age 60 and over, Starr and Hildreth[58] found the I wave decreased from 5.0 mm. to 2.2 mm., the J altitude decreased from 8.6 mm. to 5.4 mm. The decrease in I depth occurs earlier and is of greater degree than the decrease in J amplitude. The amplitudes of the H wave, mean 1.8 mm., and depth of the K wave, mean 5.2 mm., do not alter between ages 20 and 29 and age 60 and over groups. However, the relative amplitudes of the H and K waves in proportion to the I and J become significantly increased with age.

The changes in the ballistocardiogram with aging are identical with those due to coronary disease (fig. 9). They pose the question whether such changes indicate that older individuals, presumably normal, have some degree of coronary disease and impaired myocardial function. Certainly this is compatible with observations that arteriosclerosis can be demonstrated clinically in a majority of subjects over the age of 50 years.[46] Even more pertinent are the extensive pathologic studies of White, Edwards and Dry,[59] who demonstrated the presence of a severe grade of coronary artery sclerosis in well over two-thirds of subjects above the age of 50. Any middle-aged commuter running for a train will testify that his heart is not what it once was, and this apparently is what the ballistocardiogram reveals.

The factors which contribute to impairment of the ballistocardiographic waves with age are several. Primary perhaps is the decrease in cardiac strength. Among older normal subjects Jones[16] found the maximal systolic force was reduced by over one-third compared with the force in young normal subjects. The changes in the waves with aging, observed by Jones, were qualitatively as well as quantitatively almost identical with those in a group of cases with coronary disease. In addition to a decrease in cardiac force another cause for reduced wave amplitude in older subjects lies in their decreased cardiac output.

Extracardiac factors, too, may contribute to the development of ballistocardiographic abnormalities with aging, specifically, an increased width and decreased elasticity of the aorta. The capacity of the aorta in older subjects is fully double that in younger age groups, and it is to be emphasized that movement of the blood volume in the aorta contributes to the ballistocardiogram in important measure. In shock, for example, where the arterial blood volume is greatly reduced, the velocity of ejection and blood flow in the aorta is increased,[34] and the ballistocardiographic waves yield values of stroke output much greater than

the actual output determined by the Fick method.[25, 26] A similar disparity obtains in ballistocardiograms recorded in the erect position, in which circumstance the amplitude of the waves is increased despite a reduction in cardiac ejection. The importance of aortic capacity and distensibility in determining blood flow in the aorta and the complexity of aortic blood flow have received recent emphasis.[24, 26, 27, 60, 61]

It is evident that ballistocardiograms must be interpreted with reservations and with due consideration to the age of the subject. Abnormal ballistocardiograms in young individuals below the age of 40 are significant. In older subjects on the other hand, while an abnormal ballistocardiogram is not too meaningful, a normal pattern is helpful in indicating integrity in the force of ventricular ejection. It is among young subjects that the effects caused by disease processes, such as myocardial infarction, may be most clearly defined and studied.

Myocardial Disease and Heart Failure. The ballistocardiographic changes encountered in coronary disease are not specific for this condition, for any disorder associated with impaired force of ventricular ejection produces like abnormalities. As previously mentioned, these include diminution or disappearance of the I wave, significant decrease in amplitude, slurring and delayed attainment of the J peak. Such abnormalities are particularly evident in expiration which most completely reflects left ventricular ejection velocity, relatively free of right ventricular contribution to the ballistocardiogram. In addition, large diastolic waves, (the L wave and after waves) are frequently present associated with abnormal return flow to the heart, as well as a prominent H wave reflecting sudden deceleration of return flow to the heart with the onset of ventricular contraction.

These abnormalities are found not only in coronary disease, but also in rheumatic carditis, other types of myocarditis, metabolic cardiopathies such as beri-beri and myxedema, and cardiac failure. The presence of a relatively normal ballistocardiographic pattern with high amplitude J wave in subjects who are in manifest cardiac decompensation should arouse suspicion of a high output type of failure, associated with such causes as hyperthyroidism, anemia or aortic insufficiency.

Valvular Disease. Valvular lesions affect the ballistocardiogram by virtue of their influence on the velocity and quantity of ejection, and the development of myocardial failure. When cardiac decompensation ensues, the ballistocardiograph exhibits abnormalities of the I and J waves as in other types of myocardial disease, and large H, L and after waves may be present associated with abnormalities in return flow and cardiac filling (fig. 6). Mitral valvular disease does not produce any specific alterations of the ballistocardiogram, other than decreased amplitude of the IJ stroke in mitral stenosis, which reflects decreased stroke output. When mitral insufficiency is marked the amplitude of the I wave may be greatly decreased, and the J peak may be delayed.

In aortic insufficiency, the IJ stroke may be of huge amplitude. This is due not only to the augmented stroke volume, but, as the authors have observed with a velocity type of recording instrument, to a greatly increased velocity of left ventricular ejection. Whereas normally the J peak is attained 0.22 to 0.26 second from the onset of the QRS, in aortic insufficiency the J peak may be reached as early as 0.20 second. Another abnormality observed in aortic insufficiency is a widening and notching of the K downstroke, which is probably related to the altered character and direction of the blood flow in the aorta.

In aortic stenosis, the I wave may be unusually wide and large (fig. 10). Normally, the ballistic effect of expulsion of blood into the ascending aorta (which causes the I wave) is very rapidly succeeded by the counter effect of impact of the ejected blood on the aortic arch, which together with acceleration of the blood flow in the descending aorta produce the J wave. Retardation of the latter events in aortic stenosis causes the I wave to be less precipitously opposed ballistically so that it becomes accentuated.

It is to be emphasized that the ballistocardiographic changes in valvular disease occur only when the hemodynamic effects of the lesions are marked. Consequently, the ballistocardio-

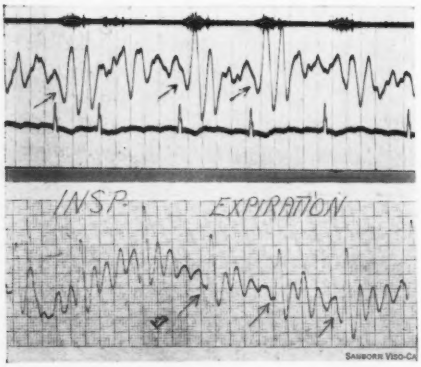

FIG. 10. Deep, slurred I wave in aortic stenosis. Top strip is that of male, age 46, with calcified aortic valve and auricular flutter. Lower strip, of another subject with aortic stenosis, shows normal I waves during inspiration, but during expiration, which best reflects left ventricular ejection, the I waves are slurred and widened.

gram is of little or no practical diagnostic importance in valvular disorders.

Abnormalities in Aortic Flow, and in Cardiac Filling and Return Flow

Abnormalities in aortic flow are revealed by changes in the K wave, and abnormalities in cardiac filling and return flow by increased prominence of the H, L and after waves. Comment has already been made on clinical disorders involving these waves under analysis of the factors involved in their origin. Although characteristic changes occur in the K waves in hypertension, arteriosclerosis and coarctation of the aorta, and in the H, L and after waves in constrictive pericarditis,[62] arteriovenous aneurysm, rheumatic heart disease and congestive heart failure,[12, 20] it may reasonably be stated that such ballistocardiographic changes are of

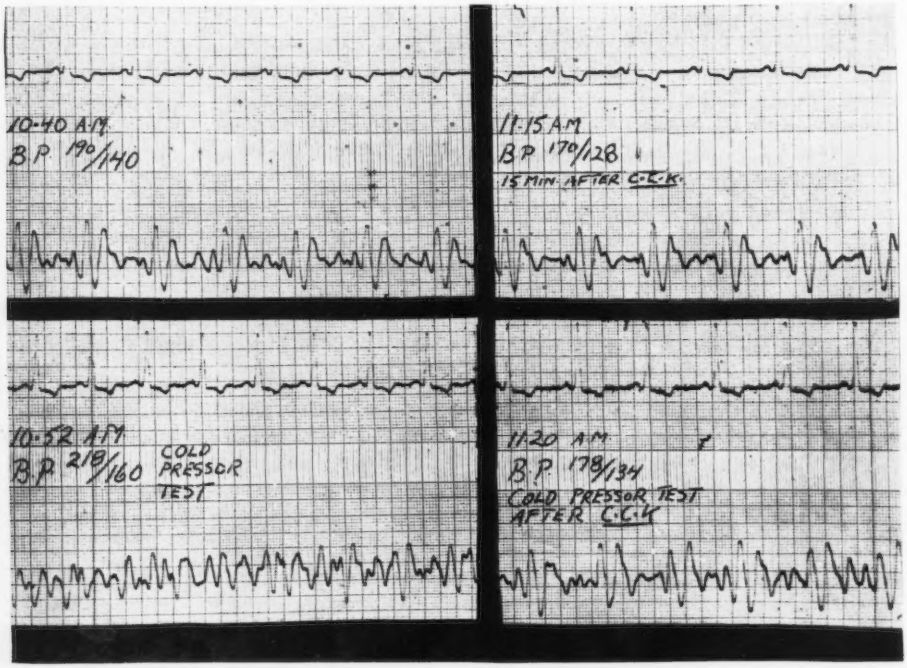

FIG. 11. Upper left strip, from subject with hypertensive heart disease, is relatively normal except for diminished I wave. Lower left strip shows development of grossly abnormal waves immediately after cold pressor test in which blood pressure rose from 190/140 to 218/160. In upper right strip after intravenous administration of hydergine (mixture of hydrogenated ergot alkaloids) tracing is similar to control. Rise in blood pressure on performance of cold pressor test was prevented and no deterioration of ballistocardiographic complexes occurred as in control test.

relatively little practical importance, and serve only to complement more fundamental diagnostic criteria.

Effect of Drugs on the Ballistocardiogram

Reflecting the force of ventricular ejection in a sensitive manner, the ballistocardiogram provides a felicitous method for the study of the effects of drugs on cardiac function (fig. 11). Among agents which have been thus investigated are digitalis,[63] quinidine,[64] epinephrine,[65] sympatholytic agents,[46] visammin,[66] nitroglycerin and other nitrites,[67] surgery and changes in blood volume,[68] and nicotine.[69, 70] The ballistocardiogram lends itself particularly well to demonstration of the effects of thyroid hormone in myxedema, thiamine in beri-beri heart disease, and in general to observation of the effects of treatment on cardiac function.[11, 71] In beriberi heart disease ballistocardiography may indeed provide an objective diagnostic sign, since response to thiamine is a clinical criterion whereby diagnosis is established.

Conclusions

It is difficult to view a new clinical procedure such as ballistocardiography in its proper perspective. Ballistocardiograms may be recorded in a variety of ways, and recording technics have been so simplified that the procedure readily lends itself to general employment. However, physical and physiologic principles are complex and as yet in part unresolved. The ballistocardiograph is unique in providing information concerning aspects of cardiac function not revealed by other diagnostic procedures, namely, an index of the force of the heart and velocity of ejection.

The regular procession of waves characterizing the normal ballistocardiogram relate to specific events in the cardiac cycle. The I and J waves, which are of principal interest, reflect the velocity and force of ventricular ejection. Phasic respiratory variation in amplitude of the I and J waves, modest in normal subjects, is accentuated in heart disease. In effect the ballistocardiogram during inspiration is a right ventricular or dextro ballistocardiogram, and during expiration a left ventricular or levoballistocardiogram. Abnormalities in the force of left ventricular ejection are masked during inspiration and may be revealed only in the expiratory phase of breathing when right ventricular ejection is reduced. This appears to explain adequately the reason for exaggerated respiratory variation in heart disease, which is perhaps the most striking feature of abnormal ballistocardiograms. Cycles exhibiting abnormal form show diminution or absence of the I wave and decreased amplitude, slurring and delayed attainment of the J peak. These evidences of impaired force of ventricular ejection are the first and most important aspect to which attention should be addressed in studying the ballistocardiogram. Abnormalities in the ballistocardiogram occur quite regularly in coronary disease and other disorders impairing myocardial function. The sensitivity of the ballistocardiographic method, however, imposes very serious limitations on its practical diagnostic value, for there is a rapidly increasing frequency incidence of abnormal ballistocardiographic patterns with advancing age, so that abnormalities are not too meaningful in older subjects.

The second factor in the ballistocardiogram which should be inspected and described is the K wave, which reflects deceleration of blood flow in the descending aorta in the latter part of systole. The K wave is shallow or absent in coarctation of the aorta and it is accentuated and attains an early trough in hypertension and arteriosclerosis of the aorta.

The third factor in analysis of the ballistocardiogram pertains to waves associated with return flow and cardiac filling, the L wave and subsequent diastolic waves. The H wave falls in this category, for although related to the onset of ventricular systole, it is due to the abrupt deceleration of blood flow returning to the heart as ventricular contraction begins. Abnormally large H, L and diastolic waves are frequently observed in myocardial disease, rheumatic heart disease, heart failure, constrictive pericarditis and arteriovenous aneurysm.

Although the ballistocardiogram supplies interesting information regarding cardiac func-

tion, it must be concluded that its specific diagnostic applications are limited. It does not replace any existing procedures in the study of heart disease, but by providing information regarding the force of contraction and blood flow, it complements other procedures in examination of the heart. Its most useful sphere of application appears to be in providing a sensitive index of the force of the heart both in heart disease and in investigating the effects of pharmacologic agents on cardiac function.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Spain, D. M., and King, D. W.: The Effect of Penicillin on the Renal Lesions of Subacute Bacterial Endocarditis. Ann. Int. Med. **36:** 1086 (April), 1952.

Thirty-three per cent of 52 untreated cases of subacute bacterial endocarditis had diffuse glomerulonephritis at necropsy. Of 25 cases treated with antibiotics, not a single case had anatomic evidence of this lesion. Focal embolic glomerulonephritis was 50 per cent lower in the treated group as compared with the untreated group. On the average, antibiotic therapy was started within one and one-half to two months from the onset of the first recognizable signs and symptoms of subacute bacterial endocarditis. The early institution of treatment may be an important factor in the elimination of these renal lesions. The type of bacteria did not appear to be a factor accounting for the difference between the treated and untreated groups. In the 25 treated cases, postmortem examination indicated that the valvular vegetations in four cases were still active with little or no evidence of healing, 10 had evidence of considerable healing and 11 appeared to be completely healed. In this treated group, none died as a result of renal insufficiency. In the nontreated group, nine cases died as a result of uremia. This was secondary in one instance to focal glomerulonephritis and in eight instances to diffuse glomerulonephritis.

WENDKOS

Geraci, J. E.: Antibiotic Therapy of Bacterial Endocarditis. I. Experiences with Terramycin in the Treatment of Subacute Bacterial Endocarditis. Proc. Staff Meet. Mayo Clin. **27:** 169 (April), 1952.

Experiences with terramycin, or a combination of terramycin and dihydrostreptomycin, in the treatment of nine patients with subacute bacterial endocarditis are presented. In five of six cases in which the combination of drugs was used, a cure was not obtained; but in the other of the six cases, the two drugs together seemed to have an enhanced bactericidal action and a cure resulted. In three cases in which terramycin was used alone, treatment was unsuccessful.

In six of the nine cases in which an organism sensitive to terramycin was obtained, there was an immediate satisfactory response to treatment, but reappearance of fever and positive blood cultures occurred in two to four weeks. In three cases in which an organism moderately sensitive to terramycin was isolated, there was no response to treatment.

Toxicity to terramycin occurred in two thirds of the cases. This consisted of anorexia, nausea and vomiting. Diarrhea was noted in one case. In three cases toxicity was serious enough to interfere with treatment.

Further experience is needed in the treatment of bacterial endocarditis with terramycin alone or in combination with other antibiotics before any final conclusions can be drawn regarding the role of this drug in the antibiotic management of bacterial endocarditis. Studies to date, however, suggest that terramycin is of limited value in the treatment of this disease.

SIMON

Bain, R. C., Geraci, J. E., DuShane, J. W., and Edwards, J. E.: Bacterial Endocarditis of the Tricuspid Valve in a 15-Month-Old Infant, Proc. Staff Meet. Mayo Clin. **27:** 180 (April), 1952.

A case is reported of bacterial endocarditis of the tricuspid valve due to *Micrococcus pyobenes tenuis* involving a 15 month old infant. The portal of entry appeared to have been the skin, which had

been involved by eczema. The clinical features of the endocarditis were manifested by fever, splenomegaly, a precordial systolic murmur and positive blood cultures. No peripheral emboli or clubbing of the fingers were apparent.

The ultimate death of the patient despite a favorable response to adequate antibiotic therapy is difficult to explain; it was probably due to the extensive pulmonary infarction noted on postmortem examination. The rarity of tricuspid valvular endocarditis in infancy is stressed.

SIMON

Bader, M., Bader, R., and Friedberg, C. K.: Causes of Failure in Treatment of Subacute Bacterial Endocarditis. J.A.M.A. **148:** 1498 (April 26), 1952.

A case of subacute bacterial endocarditis in which death occurred from congestive heart failure after three courses of therapy is carefully analyzed for the cause of failure. It was concluded that the prolonged duration of the undiagnosed and untreated disease prior to hospitalization and the beginning of treatment was responsible for the development of deep-seated lesions not accessible to otherwise adequate antibiotic therapy. Cardiac failure was due not only to the bacterial infection prior to treatment but to the continuing effect of the bacterial lesions that were not affected by antibiotic therapy despite almost a year of intensive treatment.

KITCHELL

BLOOD COAGULATION

Wynn, A., and Birbeck, A.: Prolonged Anticoagulant Therapy with Heparin. Brit. M. J. **4764:** 893 (April), 1952.

Thirty-seven patients with thromboembolic diseases were treated with heparin alone for periods up to five weeks in order to ascertain if this is an efficient and safe alternative to coumarin drugs for prolonged anticoagulant therapy, in circumstances which preclude the daily estimation of prothrombin times. Heparin was administered intravenously in nine cases, intramuscularly in 23 cases, using a concentrated aqueous solution containing 250 mg. heparin per milliliter, and by both methods in five cases.

The dose of heparin was adjusted to maintain the minimum coagulation time at approximately twice the preheparin level. In most cases this could be achieved by administration of 50 to 75 mg. intravenously every four hours, and 150 mg. intramuscularly every 12 hours. Hematomata due to intramuscular administration occurred mainly when doses larger than 150 mg. were used, when injections were given more often than every 12 hours, if the minimum coagulation time was maintained above 20 minutes, if the patient tended to bruise easily or had a considerably raised venous pressure, and in elderly patients with lax inelastic subcutaneous tissues. The development of hematomata prevented further administration of heparin in 25 per cent of the cases. Of the 37 cases, 35 suffered no further thromboembolic incidents, one patient died after a clinically typical recurrent myocardial infarction, and another experienced a mild recurrent infarction despite adequate prolongation of the coagulation times.

BERNSTEIN

Rehbein, A., Jaretzki, A. III, and Habif, D. V.: The Response of Dicumarol-induced Hypoprothrombinemia to Vitamin K_1. Ann. Surg. **135:** 454 (April), 1952.

The authors presented their results with an emulsion of vitamin K_1 in reversing hypoprothrombinemia due to prothrombin-depressing drugs. It was found that 50 mg. given intravenously were just as effective as much greater doses, even in the presence of relatively large amounts of recently administered Dicumarol. Smaller quantities, varying from 5 to 40 mg., returned a high prothrombin time to a normal or near normal range, but the response was not consistent. Doses of 0.5 to 2.5 mg. were effective in returning an excessively high prothrombin time to a safe therapeutic range, provided small doses of Dicumarol had been administered.

It was concluded that an emulsion of vitamin K_1 is a potent agent in reversing excess hypoprothrombinemia due to Dicumarol and other available prothrombin-depressing drugs. This is in contrast with water-soluble preparations of vitamin K, whose response is only partial and generally delayed 12 to 48 hours or even longer.

ABRAMSON

Hauch, E. W., Carryer, H. M., and Mathieson, D. R.: Hypersensitivity to Heparin: Report of Three Cases. Proc. Staff Meet. Mayo Clin. **27:** 163 (April), 1952.

Three instances of uncommon and unexpected reactions following the intravenous injection of heparin are presented. The reactions occurred in young people who had past histories of allergy; two had family histories of allergy. In each of the three, the allergic reaction was characterized by an itching of the conjunctiva and palate, rhinitis, and bronchial asthma. These symptoms were readily controlled by epinephrine administered subcutaneously or aminophylline administered intravenously.

The cause of this hypersensitivity is not fully understood. It is not a true allergy to heparin, since it occurs without previous exposure, tests for antibodies are usually negative, and the results of desensitization have been equivocal. Some evidence has been presented which indicates that the hypersensitivity may in some way be related to the animal source of heparin. This suggests that when anticoagulant therapy is imperative in persons who have had a reaction, a shift to a brand prepared from

a different animal source or to an entirely different anticoagulant is indicated.

SIMON

CONGENITAL ANOMALIES

Govaerts, J., Enderle, J., Henrotin, E., and Van Wien, A.: The Place of Valvulotomy in Congenital Pulmonary Stenosis. Acta cardiol. **7:** 440 (Fasc. 4), 1952.

The authors discuss the incidence, diagnosis, differential diagnosis and treatment of the three common congenital lesions associated with pulmonary stenosis which are amenable to surgery.

In pure pulmonic stenosis and in pulmonic stenosis with atrial septal defect (trilogy of Fallot) the operation of choice is Brock's valvulotomy. Experience has shown that in these conditions creation of an arteriovenous shunt according to Blalock or Potts is not followed by improvement and may precipitate heart failure. Valvulotomy is also indicated in Fallot's tetralogy if the stenosis is valvular in type. The indication for this type of operation may be doubtful in the presence of infundibular stenosis, for anatomic and technical reasons. However, from the pathophysiologic standpoint it is preferable to a shunt operation, since it relieves the most important of the four lesions of the tetralogy, while the latter operation creates an additional one, which eventually may lead to heart failure.

The problem is illustrated by the report of a case of typical tetralogy, where an anastomosis of the Blalock type was intended but could not be completed for anatomic reasons. Valvulotomy was then performed without difficulties and was followed by considerable improvement.

PICK

Doerr, W.: A Formal Principle of Association of Developmental Anomalies of Venous and Arterial Ventricular Ostia. Ztschr. Kreislaufforsch. **41:** 269 (April), 1952.

Malformations of the venous and arterial ostia of the ventricles frequently occur in association. This has been shown by R. F. Shannon in his extensive studies on the development of heart in pig embryos, and is frequently seen in human pathology. In the course of transformation of the cardiac loop into its final form, the torsion and absorption of the bulbus into the basal parts of the ventricles seems to represent a "weak spot" of normal cardiac developments. When the arterial end of the loop (bulbus and truncus cordis) is detained on its physiologic pathway from right to left, and from the frontal to the parasagittal plane, defects may result in the intraventricular septum which in turn lead to hemodynamic conditions favorable for the development of overriding of the aorta or pulmonary artery, asymmetric division of the truncus, or complete transposition of the two big vessels. Application of such a common principle is helpful for the understanding of the pathogenesis of lesions like Eisenmenger's complex, Fallot's tetralogy, the Taussig-Bing syndrome, and other transposition complexes, for which, according to the author, a satisfactory explanation is lacking.

PICK

CONGESTIVE HEART FAILURE

Reynolds, T.: Sweat Sodium Levels in Congestive Heart Failure. Proc. Soc. Exper. Biol. & Med. **79:** 118 (Jan.), 1952.

In this study, sweat sodium concentrations were investigated by a method applicable to patients with heart failure. Congestive heart failure patients were studied while retaining edema fluid, before and after Mercuhydrin injection, and in a few instances when recompensated. There was no evidence that increased adrenal electrolyte hormone activity contributed to the sodium retention of heart failure. The mean sweat sodium concentration of one group of congestive heart failure patients was significantly higher than that of the controls. Mercuhydrin did not affect sweat sodium concentration. In addition to the adrenal cortex, there may be numerous nonendocrine factors that affect sweat electrolyte composition.

MINTZ

Iseri, L. T., Alexander, L. C., McCaughey, R. S., Boyle, A. J., and Myers, G. B.: Water and Electrolyte Content of Cardiac and Skeletal Muscle in Heart Failure and Myocardial Infarction. Am. Heart J. **43:** 215 (Feb.), 1952.

In a previous report, the authors postulated that during the development of cardiac failure, the cells lost potassium and sodium and gained water presumably because of activation of osmotically inert cellular base. In the present study, the water and electrolyte content of myocardial and skeletal muscle obtained at autopsy was determined in patients dying of congestive failure or myocardial infarction and in patients dying of noncardiac causes.

Myocardial blocks from standard sites in the left ventricle and blocks from the pectoralis major were analyzed for water, sodium, potassium, chloride, magnesium, and phosphorus. In 16 control patients and 14 patients with uncomplicated left ventricular hypertrophy without evidence of congestive failure, the average content of water and each electrolyte was identical, 78.8 Gm. water, 4.96 mEq. sodium, 8.32 mEq. potassium, 4.04 mEq. chloride, 0.445 mEq. magnesium, and 3.88 mEq. phosphorus per 100 Gm. of wet tissue. In eight patients with congestive failure, there was a significant reduction in potassium, 6.78 mEq., but no significant change in water, sodium, chloride, magnesium or phosphorus The total intracellular base concentration was sig-

nificantly reduced in cardiac and skeletal muscle mainly from potassium loss. In seven patients with recent myocardial infarction, infarcted myocardium showed a marked but proportionate increase in sodium and chloride, suggesting that these elements enter the infarcted myocardium as neutral sodium chloride. There was a marked reduction of potassium, magnesium, and phosphorus, reflecting primarily losses from injured myocardium. In noninfarcted myocardium, the five electrolytes gave values intermediate between the values obtained from infarcted segments and those from normal controls.

It is probable that acute ischemia without necrosis was responsible for the chemical changes in areas beyond the gross infarct. The authors suggest that serial biopsies of skeletal muscle during life might serve as a useful, though indirect, index of changes in the concentration of total base and potassium in patients with congestive failure.

HELLERSTEIN

Heyer, H. E., Howard, C. H., Willis, K. W., and Pickle, A. C.: Alterations of the Rapid Filling Phase in Congestive Heart Failure. Am. Heart J. **43:** 206 (Feb.), 1952.

The authors present electrokymographic studies of the duration and contour of the various phases of the cardiac cycle in 31 normal subjects and 19 nondigitalized patients with nonvalvular congestive failure. The only significant finding in the latter group was a definite shortening of the phase of rapid filling, as compared with the normal subjects. In both groups there was little or no influence of rate on the duration of rapid filling. The mean duration of rapid filling in the normal group was 0.174 second ± 0.043, compared with a mean duration of 0.11 second ± 0.010 for the group in failure. The increased rapidity of rapid filling in congestive failure would appear to be related primarily to the increased pressure-filling gradient present in the failing heart at the onset of ventricular diastole. As a measure of the abnormal hemodynamics present in diseased hearts, the systematic recording of the duration of rapid-filling phase and its comparison with normal values would appear to be of objective value in assessing the presence of an increased atrioventricular pressure-filling gradient due to heart failure.

HELLERSTEIN

Goldman, R., and Bassett, S. H.: Diurnal Variation in the Urinary Excretion of Neutral Lipid-Soluble Reducing Steroids in Congestive Cardiac Failure and Cirrhosis of the Liver with Ascites. J. Clin. Investigation **31:** 253 (March), 1952.

There is a normal cycle of excretion of neutral lipid-soluble reducing steroids with a maximum between 7:00 a.m. and 11:00 a.m., and a minimum during the night. This resembles the normal excretory cycle of other urinary constituents. Since in congestive heart failure and in hepatic cirrhosis with ascites there is a reverse diurnal cycle of water and sodium excretion, this investigation was designed to determine whether the excretion of steroids was also altered in these conditions. Although the total average 24-hour excretion of steroids was essentially within normal limits, there was an alteration in distribution. In 14 patients with cardiac failure and in 12 with cirrhosis of the liver, and ascites maximum excretion of these steroids was most commonly observed in the afternoon or during the night. Since the excretion of steroids in cirrhosis and cardiac failure was proportional to the excretion of creatinine, it is suggested that the steroid excretion may be proportional to the glomerular filtration rate. Abnormal patterns of diurnal urinary excretion of water, sodium and creatinine are associated with similarly abnormal patterns of steroid excretions.

WAIFE

Mokotoff, R., Ross, G., and Leiter, L.: The Electrolyte Content of Skeletal Muscle in Congestive Heart Failure; A Comparison of Results with Inulin and Chloride as Reference Standards for Extracellular Water. J. Clin. Investigation **31:** 291 (March), 1952.

If one accepts the "chloride space" or "corrected chloride space" as the reference standard for extracellular water, it would appear that the cardiac patient with heart failure has a loss of intracellular potassium and a gain of intracellular sodium; however, with inulin as a reference standard, there is no change in the intracellular electrolyte composition in heart failure as compared with the normal. The true value for extracellular water is not evident in this present study.

WAIFE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Lindsay, S., Chaikoff, I. L., and Gilmore, J. W.: Arteriosclerosis in the Dog. Spontaneous Lesions in the Aorta and the Coronary Arteries. Arch. Path. **53:** 281 (April), 1952.

The authors studied canine arteriosclerosis, most of their dogs being 12 or 13 years old. In a group of 14 such dogs, five had myocardial failure closely resembling that occurring in humans; of these, two had gross myocardial infarctions. Spontaneous arteriosclerosis is seen characteristically throughout the thoracic and lumbar aorta as a local fibroblastic thickening of the intima, not associated at any time with the deposition of cholesterol. There is also focal destruction of the elastica in the media with local cyst formation and mucopolysaccharids deposit. The authors consider the experimentally induced atherosclerosis (cholesterol, thiouracil) as an entirely different process and are convinced that the spontaneous arteriosclerosis of dogs is the result simply of aging.

Study of the coronary arteries revealed hyaline thickening of the intima, cytoplasmic vacuolation in the media, and in two cases, acute or subacute occlusion of the main coronary arteries, due apparently to hemorrhage originating within the thickened vessel wall. All of these occluding lesions were free of cholesterol.

GOULEY

Herman, E. F., and Akman, L. C.: Intra-arterial Infusion in the Treatment of Shock Resulting from Coronary Occlusion. Am. Heart J. **43:** 264 (Feb.), 1952.

The authors treated eight patients with coronary shock by intra-arterial (brachial) infusion of blood or plasma. The patients were in shock for 3 to 28 hours before infusion. Up to 1000 cc. of blood or plasma were given at a rate of 75 to 100 cc. per minute. Elevation of arterial pressure occurred in four patients and became manifest about 20 to 40 minutes after completion of the infusion, continuing to rise slowly for one to three hours. One patient was discharged from the hospital and survived 10 months after treatment. There was no increase in pulmonary congestion during infusion, but one patient developed ventricular fibrillation shortly after infusion. The authors recommend earlier institution of treatment, before an advanced state of shock occurs.

HELLERSTEIN

Sundin, T.: The Cardiac Hypoxemia Test (CO_2, O_2), its Accuracy and Normal Variability. Acta med. scandinav. **142:** 82 (Fasc. II), 1952.

The author has tested the accuracy and the normal variations of the cardiac hypoxemia test using the technic of Malmstrom. This procedure consists of recording the electrocardiogram at rest and then repeating it immediately after the patient has breathed a mixture of 4.5 per cent carbon dioxide, 6.5 per cent oxygen and 89 per cent nitrogen for 10 minutes in a closed system. A group of 60 normal men between the ages of 20 and 30 years, and another of 49 normal men between the ages of 40 and 50 years were studied. In the test of persons aged 40 to 50 years, the electrocardiogram recorded at rest normally showed slight elevation of the S-T segment above the isoelectric level. After hypoxemia, the S-T segment tended to creep below the isoelectric level, except in lead CR_2 where it remained above that level due to the high resting S-T elevation.

In the test of subjects aged 20 to 30 years, marked elevation of the S-T segment was present in all leads at rest, and it was still above the isoelectric level after hypoxia, except in lead III where a negligible depression appeared. The mean heart beat at rest in the older group was 78.6 ± 1.9 beats per minute; after exercise it was 101.2 ± 1.7 beats per minute. In the younger group, the corresponding heart rates were 67.0 ± 1.6 and 96.1 + 1.6 beats per minute. The smaller heart-rate increase was thus associated with the greater S-T depression. This is considered an argument against the view that T-wave changes and S-T depression in hypoxemia are due to a high heart rate. Duplicate determinations were found to reveal only a very small error in this hypoxemia test, and the procedure is considered sufficiently accurate for clinical purposes. None of the normal subjects displayed any T-wave abnormalities.

ROSENBAUM

Borden, C. W., Ebert, R. V., and Wilson, R. H.: Anoxia in Myocardial Infarction and Indications for Oxygen Therapy. J. A. M. A. **148:** 1370 (April 19), 1952.

Despite the universal practice of giving oxygen to patients with myocardial infarction, little information is available regarding the oxygen saturation of the hemoglobin of the arterial blood in this disease. Therefore, a group of 23 patients with myocardial infarction were studied from this standpoint. The mean value of arterial oxygen in those patients without pulmonary edema or shock was 80.8 per cent. On the basis of these findings, it is apparent that the use of oxygen therapy is mandatory in those patients with pulmonary edema or shock, and of questionable value in patients with uncomplicated myocardial infarction. It is felt that if oxygen is used in the latter group, it should preferably be given in high concentration by mask rather than in the lower concentration obtained by the use of an oxygen tent.

KITCHELL

Miller, A. J., and Baker, L. A.: l-Arterenol (Levophed) in the Treatment of Shock Due to Acute Myocardial Infarction. Arch. Int. Med. **89:** 591 (April), 1952.

Seven patients with acute myocardial infarction complicated by severe or profound shock were treated with l-Arterenol intravenously. Significant arterial blood-pressure elevations were attained in four of the seven patients. In no instance was any untoward effect noted on the prevailing cardiac rhythm, the state of congestive heart failure, or the subjective status of the patient.

While the administration of l-Arterenol in this small series of patients did not give evidence of any untoward effects, its use should still be approached with caution. Further observations are indicated with respect to its advantages and its disadvantages. Likewise, from this limited experience, no conclusion can be drawn in regard to the bearing this treatment had on ultimate mortality. The results are sufficiently encouraging to justify further careful clinical evaluation of the use of l-Arterenol in cardiogenic shock following recent myocardial infarction.

BERNSTEIN

Newman, L. B., Andrews, M. F., Koblish, M. O., and Baker, L. A.: Physical Medicine and Rehabilitation in Acute Myocardial Infarction. Arch. Int. Med. **89:** 552 (April), 1952.

A program of rehabilitation for patients suffering from acute myocardial infarction is outlined in detail. It involves the coordination of psychotherapeutic and physical and occupational therapeutic activities. It is felt that such a program makes for better physician-patient relationship, decreases the tendency to anxiety, and prevents general physical deconditioning of the patient. Ambulation is accomplished with less physiologic disturbance and apprehension, and strength and endurance are recovered more rapidly. The authors have been impressed by the finding that the incidence of anxiety neurosis following recovery from acute myocardial infarction is much less.

The rehabilitation program contributes to more satisfactory recovery and adjustment on the part of the patient. Whenever possible, patients who should not return to their former type of occupation are seen by the vocational adviser regarding new employment. If the need arises, a social service worker should evaluate the home situation. Both the physician and the patient will have a much clearer concept of the patient's physical and mental capabilities, resulting in more objective and realistic plans for the future.

BERNSTEIN

Halonen, P. L., and Taipale, E.: Angina Pectoris, a Symptom of Spontaneous Hypoglycemia. Cardiologia **20:** 193 (Fasc. 4), 1952.

The authors report five cases with angina pectoris in whom pain appeared only while fasting, in three on exercise, and in two also at rest. Pain could never be elicited for several hours following a meal, and was relieved by intake of food or sugar. Clinical studies failed to reveal any other abnormalities except unusually low blood sugar values two to three hours following a glucose-tolerance test. While the blood sugar was at its lowest level, the patients experienced a chest pain similar to that described in their history. It appears that spontaneous hypoglycemia can occasionally cause angina pectoris. This possibility has to be remembered, and glucose-tolerance tests should be performed in instances of atypical angina pectoris.

PICK

ELECTROCARDIOGRAPHY

Segers, M., Regnier, M., and Delatte, E.: Sudden Beginning of Electrocardiographic Pattern of "Right Ventricular Preponderance." Acta cardiol. **7:** 63, 1952.

The authors discuss eight clinical cases in which the electrocardiographic pattern of "right ventricular preponderance" either appeared or disappeared suddenly. This electrocardiographic change took place without any modification of blood pressure and of the cardiac silhouette upon x-ray. The authors believe that the pattern of "ventricular preponderance" is not caused by ventricular hypertrophy but is due to a special type of intraventricular block.

LUISADA

Moia, B., Malinow, M. R., and Bandino, C.: Sectional Changes of Venous Pressure Studied Clinically by Catheterization. Acta cardiol. **7:** 1, 1952.

Several patients, with and without congestive failure, were studied by introducing a catheter into the right auricle and then measuring venous pressure during retraction of the catheter. A water manometer was employed. The average right auricular pressure was below 60 mm. of water in 15 cases without right heart failure. In five of them, the pressure was uniform throughout, while, in the other 10, 20 to 50 mm. increase was noted at the axilla or in the arm. Inspiration decreased venous pressure above that area, very seldom below it. Abdominal compression failed to increase venous or right auricular pressures by more than 20 mm. of water. The average right auricular pressure was above 70 mm. of water in six cases with right heart failure. A similar pressure was present all along the venous system. Deep inspiration was followed by increased pressure in the right auricle and in the central veins. Abdominal compression caused an increase of pressure in both the central and the peripheral veins of more than 20 mm. of water. The authors deny the existence of a gradient of pressure in the venous system and find normal venous pressure as long as there is no heart failure.

LUISADA

Vazifdar, J. P., and Levine, S. A.: Benign Bundle Branch Block. Arch. Int. Med. **89:** 568 (April), 1952.

Thirty-one instances of benign bundle branch block were found in a consecutive series of 452 cases of bundle branch block (left or right) observed in office practice during the years 1922 to 1951. The benign group had no other subjective or objective evidence of heart disease. They have been followed for many years (5 to 29 years) and have remained well. The cause of the block is obscure. The authors suspect such patients may have acquired the electrocardiographic abnormality as a result of some intercurrent, otherwise harmless infection which left no other injury to the heart. The physician should make light of this condition and permit such patients to carry on normal duties.

In a study of 62 patients with death from coronary artery disease who also had bundle branch block, it was found that those with right bundle branch block lived three or more years longer than

those with left block, after the onset of either cardiac symptoms or bundle branch block. There were numerous patients having coronary artery disease with bundle branch block who carried on satisfactorily for 10 to 25 years after the abnormal electrocardiograms were first detected. The inference is that the prognosis need not be grave in these circumstances.

BERNSTEIN

Wenger, R.: The Sagittal Vectorcardiogram with Special Reference to the Vectorial Interpretation of the Esophageal Electrocardiogram. Ztschr. Kreislaufforsch. **41:** 298 (April), 1952.

The contour of sagittal vectorcardiograms was studied and compared with esophageal electrocardiograms obtained at different levels. Normally, the sagittal vector loop develops in caudal and more or less ventral direction. In the majority of normal instances this correlates well with the contour of ventricular complexes found in esophagrams. However no correlation was found between shape and direction of auricular loops and contour of P waves in leads obtained at auricular levels. Upright QRS complexes in esophageal leads at auricular and higher levels correspond to a marked deviation of the QRS loop in cranial direction as found in left ventricular hypertrophy, in the presence of left bundle branch block, with tricuspid atresia, and in posterior wall infarction. Cases with right bundle branch block usually show pronounced notching of QRS in the esophageal leads which is a reflection of marked irregularities of the sagittal vector loop. The study and more detailed analysis of these complicated figures may provide a method to determine the sequence of ventricular activation in right bundle branch block.

PICK

Böckl, E. M., and Schaefer, H.: Attempts to Calculate Vectors from Precordial Leads. Ztschr. Kreislaufforsch. **41:** 310 (April), 1952.

The authors present investigations concerning the validity of the concept that precordial leads are projections of the integrated spatial vector upon the horizontal plane. The QRS area of each of the conventional 6 chest leads was expressed in the form of a vector, the magnitude of which was reduced to a size corresponding to a distance of 1 cm. between recording electrode and the assumed center of the heart. For the determination of the latter, the usual method, namely determination of the localization of diametral, mirror image, QRS patterns over the thorax, proved inadequate. According to the authors the point of zero potential is defined by the center of a semicircle connecting the positions of those electrodes which record the largest and the smallest potential of the precordium.

Using this method, the direction of the integrated QRS vector in its projection upon the horizontal plane can be determined from precordial leads with an error of ± 7.5 degrees, and its magnitude with an error of ± 16 per cent. It is concluded that for practical purposes all recorded potentials created by the heart can be represented by a single vector, the horizontal projection of which is the precordial leads. The assumption of a homogeneous electrical conductor with a geometrically simple surface, and of a central position of the heart within this conductor are simplifications which, within reasonable limits, do not interfere with the accuracy of interpretations of the vectorcardiogram.

PICK

Hertzman, V. O., and Mathisen, A. K.: Observations on the Electrocardiogram in Surgically Treated Pulmonary Tuberculosis. Am. Rev. Tuberc. **65:** 443 (April), 1952.

A series of 68 patients undergoing collapse therapy of various types for pulmonary tuberculosis was studied before and after surgery. Eleven patients had electrocardiographic changes following surgery. In two cases the electrocardiogram, previously abnormal, became normal following surgery. In three cases the abnormal electrocardiograms remained abnormal. In only five cases was the surgical procedure followed by the first appearance of electrocardiographic abnormalities. In four of these cases the abnormalities were similar, that is, low or flat T_1, associated with a semivertical or vertical electrical axis.

These electrocardiographic changes reflect pulmonary hypertension either secondary to the underlying tuberculosis or to collapse therapy, or changes in the electrical and/or anatomic axis of the heart. There were no consistent transitional-zone or electrical-axis changes in any of the groups studied. The electrical position of the heart is particularly important in evaluating the electrocardiogram in patients who have had chest surgery. The value of multiple precordial and augmented unipolar limb leads in such cases has again been demonstrated.

BERNSTEIN

Soffer, A., Yu, P. N. G., Epstein, M. A., and Olson, E. S.: Comparison of the Resting Electrocardiogram and the Ballistocardiogram during Prolonged Periods of Observation. Am. J. M. Sc. **223:** 378 (April), 1952.

The authors studied a group of 11 patients who were experiencing the anginal syndrome due to coronary atherosclerosis; each of these patients manifested abnormal electrocardiographic changes in the Master two-step test. During a period of eight and one-half months, repeated electrocardiograms and ballistocardiograms were obtained in order to determine whether the latter would provide a more sensitive method for following the course of the disease in these patients. In the resting patients, nine had an abnormal ballistocardiogram, while in

only four was the resting electrocardiogram abnormal. Therefore it was concluded that the ballistocardiogram more frequently evidenced abnormalities than the resting electrocardiogram and compared favorably with the exercise electrocardiogram. In the electrocardiogram evaluations, seven patients showed improvement during the period of observation; one showed no change and three showed deterioration. These trends were present in both the resting and exercise tracings. The ballistocardiogram revealed no change in 8 of the 11 patients; one improved, and in two patients, the complexes became more irregular. The changes noted on the ballistocardiogram were more difficult to interpret than the familiar alterations in the electrocardiogram. As a method for measuring the progress of patients with coronary artery disease, the ballistocardiogram is a less valuable agent than the electrocardiogram.

SHUMAN

Gmachl, E.: On Electrocardiograms with Prevalent Inverted Deflections in All Standard Leads. Cardiologia **20:** 249 (Fasc. 4), 1952.

Among 15,000 electrocardiograms, the authors found 16 instances with inverted QRS complexes in leads I to III. Seven of them had myocardial infarction; seven others showed clinical and roentgenologic evidence of marked right ventricular hypertrophy and severe myocardial damage; in one case no clinical data were available; and in another there was chronic pulmonary disease but no clinical or radiologic signs of cardiac involvement. The latter case demonstrates that the electrocardiographic pattern under question is not necessarily associated with heart disease, as claimed in some previous studies, but may also be due to an abnormal position and rotation (in clockwise direction) of the heart.

PICK

HYPERTENSION

Clayton, G. W., and Hughes, J. G.: Variation in Blood Pressure in Hospitalized Children. J. Pediat. **40:** 462 (April), 1952.

Seven hundred and twenty-nine blood pressure determinations were made in 96 children, most of whom were admitted for elective surgical procedures and mild infections. None was admitted for the diseases ordinarily associated with hypertension. There was great variation among the children in the degree of fluctuation or stability of their blood pressure. There were three patterns of response. The most common was for the blood pressure to be higher in the admitting room and then progressively lower on the ward. The next most common was for the pressure to rise in the initial hours on the ward and then become progressively lower. The third pattern consisted of relatively little fluctuation. The factors which influenced the blood pressure the most were emotional tension incident to hospital admission and the anticipation of separation from parents. The initial pressure in some cases was 30 to 40 mm. Hg higher than the stabilized pressure. Other factors causing blood pressure variation were: awakening, anger, eating, painful procedures, physical activity, recreation, postoperative state and visits of parents. These variations were never as great as those encountered in the initial hours after admission. It was interesting to see that acutely ill children had a more stable blood pressure pattern than those who were only mildly ill.

The authors conclude that in the interpretation of blood pressure in hospitalized children, emotional and environmental factors must be considered. Serial readings, rather than single determinations, are necessary in order to ascertain the truly stabilized blood pressure.

MARGOLIES

Gibbons, T. B., and Chapman, C. B.: The Effect of Sweating on Normo- and Hypertensive Subjects. J. Lab. & Clin. Med. **39:** 420 (March), 1952.

The plasma and total blood volumes, the thiocyanate space, and the antipyrine space were found to be normal in patients with essential hypertension. Dehydration by sweating, unaccompanied by a large loss of electrolytes, has no lasting effect in lowering the blood pressure in hypertensive patients.

MINTZ

de Takats, G.: Limitations of Sympathectomy in Treatment of Diastolic Hypertension. J. A. M. A. **148:** 1382 (April 19), 1952.

The initiating and maintaining factors of human diastolic hypertension have been described. Neurogenic, corticoadrenal, and renal factors form a vicious circle which can be broken at several points, notably by sympathectomy. This operation, however, has definitely limited indications, and in the author's series of cases has only been undertaken regularly in patients whose status is readily defined.

One indication for this operation is intermittent hypertension that can be reduced to normal by bed rest or by barbiturates, and which is beginning to show the earliest signs of vascular damage in the retina, heart, or kidney. The second indication is that of the middle-aged hypertensive patient who shows diffuse vascular damage and whose moderately elevated diastolic pressure of 100 to 110 mm. Hg shows a consistent rise in spite of medical management. The third indication is hypertension in the rapidly progressive premalignant phase when the diastolic pressure is fixed but no advanced renal damage has occurred. The fourth indication, which is rare, is intractable headache resulting from hypertensive encephalopathy in patients with advanced renal damage. This of course is only a palliative procedure to relieve symptoms.

In a five-year follow-up of a small number of

closely observed patients, improvement in results could be expected mainly by attention to the renal factor. The primary object of the operation is arrest of cardiovascular disease and not lowering of blood pressure, which in itself does not mirror organic vascular damage. While newer diets and drugs may replace the necessity for operation in certain persons, sympathectomy has a definite, well-defined place in the treatment of human essential hypertension.

KITCHELL

Finnerty, F. A., Jr.: Hypertensive Toxemias of Pregnancy. A Simplified Method of Management Using a Purified Extract of Veratrum Viride. New England J. Med. **246:** 646 (April 24), 1952.

This report is concerned with the results of treatment of 122 cases of hypertensive toxemias of pregnancy with aqueous injectable Vergitryl, a purified extract of Veratrum viride containing known concentrations of the hypotensive ester alkaloids, germitrine, neogermitrine and germidine. In eight cases of convulsive toxemias, the drug was given intravenously in a solution of 1.5 units of Vergitryl to 20 cc. of 5 per cent dextrose in water. The dose is determined by actual response to slow careful administration. A polyethylene catheter left in the vein permits subsequent doses at 40-minute to two-hour intervals. The results were excellent in four patients, good in two, and fair in the remaining two.

Vergitryl was administered intramuscularly in 114 cases of nonconvulsive toxemia of pregnancy with results which were excellent in 92, good in 18, fair in three, and poor in only one. Increased salivation, nausea, vomiting, and diarrhea were the chief toxic effects. Nausea and vomiting, which occurred in 16 per cent of the patients, was readily controlled with moderate doses of pentobarbital sodium. The author reports one patient who received, by error, 0.75 units of Vergitryl undiluted, intravenously. Profound vasomotor collapse and bradycardia followed, but four doses of atropine sulfate (1 mg. each) given intravenously at five-minute intervals produced a prompt reversion to normal. A patient with hypertensive encephalopathy is mentioned; she received erroneously a dose of 3.75 units of Vergitryl intramuscularly. Marked collapse followed in 15 minutes. Atropine sulfate was ineffective, but intravenous Neosynephrin and ephedrine restored a normal arterial pressure, and recovery was uneventful.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Werko, L., Ek, J., Bucht, H., and Eliasch, H.: Correlation Between Renal Dynamics, Cardiac Output and Right Heart Pressures in Mitral Valvular Disease. Scandinav. J. Clin. Lab. Investigation **4:** 15 (no. 1), 1952.

In 16 cases of mitral valvular disease without heart failure at rest the cardiac output, plasma volume, blood pressure in the systemic and pulmonary circulation were determined. The renal clearances for para-aminohippurate, inulin and creatinine were determined and the renal blood flow and filtration fraction calculated. The pressures in the pulmonary circulation were markedly increased, the cardiac output was reduced and the plasma volume slightly raised as compared with the corresponding values in a normal group. The para-aminohippurate clearance was lowered, the inulin clearance remained within normal limits or low and the filtration fraction was increased. There was a fair correlation between the renal plasma flow and the filtration fraction on the one hand, and the pressure in the pulmonary artery on the other. The right auricular pressure was not increased, nor was there any correlation between the renal blood flow and the auricular pressure. The total renal resistance was increased. In cases with mitral valvular disease the blood flow is deviated from the kidneys owing to changes within the kidneys themselves even before any signs of heart failure have appeared.

BERNSTEIN

Donovan, T. J., Hufnagel, C. A., and Eastcott, H. H. G.: Techniques of Endocardial Anastomosis for Circumventing the Pulmonic Valve. J. Thoracic Surg. **23:** 348 (April), 1952.

The authors described a means of constructing a new pulmonary artery in dogs. Tracheal tubes, lined with a graft of the inferior vena cava, and polyethylene tubes were used in the procedure. After an incision was made in the right ventricle, one end of the tube was introduced through it into the chamber. The other was sutured to the distal end of the left pulmonary artery after the proximal portion of this vessel was ligated.

The operation was performed on 15 animals, 11 of whom survived. These were subsequently sacrificed and at autopsy all grafts but two were found to be occluded. It was believed that the failure of the shunts to remain permanently patent was due to the lack of sufficient pressure gradient on ligation of the left pulmonary artery and to intrinsic weakness of the venous-lined tubes.

ABRAMSON

Davis, H. A., Gordon, W. B., Hayes, E. W., Jr., and Wasley, M. T.: Effects Upon the Lung of Varying Periods of Temporary Occlusion of the Pulmonary Artery. Arch. Surg. **64:** 464 (April), 1952.

An attempt was made to determine the sensitivity of the lungs of monkeys to varying periods of ischemia produced by temporary, complete occlusion of one pulmonary artery. It was found that periods up to 48 hours did not cause irreversible structural changes in the ipsilateral lung. Beyond this time the alterations were more likely to become permanent. Such results were interpreted as indicating

that pulmonary tissue possessed a considerable resistance to ischemic anoxia, much greater than that demonstrated by other vital organs.

ABRAMSON

Lemley, J. M., and Meneely, G. R.: Distribution of Tissue Fluid in Hearts of Rats Subjected to Anoxia. Am. J. Physiol. **169:** 61 (April), 1952.

Using radioactive sodium, total water and extracellular water of the ventricles was increased as a result of exposure to anoxia. Intracellular water was reduced. Skeletal muscle did not show similar changes.

OPPENHEIMER

Weissel, W., and Vetter, H.: Investigations by Cardiac Catheterization on Variations of the Electro-Pressoric Latency in Disturbances of Rhythm. Cardiologia **20:** 160 (Fasc. 3), 1952.

The authors studied alterations of the time of isometric contraction of the ventricles effected by premature beats occurring during cardiac catheterization in man. Data were obtained by measuring the time intervals from the beginning of the QRS complex to the onset of pressure rise in the ventricles, the aorta, and the pulmonary artery. These time intervals were seen to increase with a premature contraction and to shorten in the first beat succeeding the premature beat. The degree of alteration was dependent on the degree of prematurity. In two cases with auricular fibrillation, the respective time intervals were found to vary inversely with the duration of the preceding cycle, becoming longer with shortening of the cycle and vice versa.

PICK

Ankeney, J. L.: Interrelations of Pulmonary Arterial, "Capillary" and Left Atrial Pressures Under Experimental Conditions. Am. J. Physiol. **169:** 40 (April), 1952.

At the end of ventricular systole "pulmonary capillary" pressures are 1.5 to 3.7 mm. greater than found in the left atrium. Changes produced in left atrial pressures are accompanied by like changes in the pulmonary capillary pressures. Pulmonary capillary pressures measured by a catheter properly impacted in a peripheral pulmonary artery are independent of pulmonary artery or aortic pressures. To be valid pulmonary capillary pressure pulses must be devoid of phasic changes.

OPPENHEIMER

Walton, R. P., Goldberg, L. I., Gazes, P. C., Leary, J. S., Ezell, H. K., Hanna, C. B., and Prystowsky, R. P.: Effects of Hyperpyrexia on the Heart in situ: Studies with Dicumarol, Dinitrophenol and External Heat. Am. J. Physiol. **169:** 78 (April), 1952.

Both external infrared or diathermy, on the one hand, and Dicumarol or dinitrophenol, on the other, are able to produce an increase in the force of cardiac contraction. These changes are not due to variations in venous or arterial pressures, or heart size. The stimulating action of Dicumarol and dinitrophenol is similar. In higher doses both depress the heart. External heat or the two calorigenic drugs produce similar electrocardiographic changes. Large fatal doses of intravenous Dicumarol decrease the height of R to 10 per cent of control values in the preagonal period. This last pattern is quite different from the other agents.

OPPENHEIMER

Brown, E. B., Jr., and Miller, F.: Ventricular Fibrillation following a Rapid Fall in Carbon Dioxide Concentration. Am. J. Physiol. **169:** 56 (April), 1952.

Dogs were allowed to breathe 30 to 40 per cent carbon dioxide for four hours while under anesthesia. Rapid reduction of alveolar carbon dioxide tension produced ventricular fibrillation and death in 11 of 15 dogs. The four surviving animals exhibited arrhythmias. Two animals in whom the carbon dioxide was slowly reduced survived without arrhythmia. The authors stress the importance of these findings in anesthesia.

OPPENHEIMER

Lemley, J. M., and Meneely, G. R.: Effects of Anoxia on Metabolism of Myocardial Tissue. Am. J. Physiol. **169:** 66 (April), 1952.

Heart tissue homogenates from rats subjected to anoxia had only a 50 per cent uptake of oxygen as compared with control animals. There were small but significant reductions in coenzyme I and cytochrome *c* in anoxic hearts. Lactic acid and dehydrogenase were unchanged. Aqueous extracts from boiled hearts of control rats restored the oxygen use of heart homogenates from rats which had been exposed to anoxia. The authors conclude that the loss or inactivation of a heat-stable substance accounts for the reduced oxygen use. They consider that the decreased oxygen utilization was not caused by destruction of respiratory enzymes but by a decrease in factors needed for normal activity.

OPPENHEIMER

Charbon, B. C., and Adams, W. E.: A Study to Determine the Effect of Prevention of Overdistension of the Remaining Lung Tissue on the Elevated Right Ventricular Pressures, Following the Resection of Lung Tissue in Dogs. J. Thoracic Surg. **23:** 341 (April), 1952.

The authors studied right ventricular pressures in dogs after removal of up to 85 per cent of lung tissue. In all animals in which overdistension was prevented, the average pressure was lower by 28 per cent, as compared with the control operated group. However, when removal of all lung tissue but the left upper lobe was carried out in steps, the

mortality was 100 per cent in those dogs in which overdistension was prevented, while in the group in which this was not done, some of the animals survived for weeks. The explanation of the difference was that when overdistension was prevented, the remaining pulmonary vascular bed did not have an opportunity to enlarge gradually.

ABRAMSON

Tomaschett, P.: Dysproteinemic Myocardosis in Diabetes Mellitus. Cardiologia **20:** 215 (Fasc. 4), 1952.

The author studied blood protein patterns in 50 diabetic patients below the age of 40, in whom electrocardiographic and clinical findings suggested the presence of degenerative myocardial changes. With one exception, all showed dysproteinemia of some degree, which was found to be in direct proportion to the severity of the metabolic disorder and was especially pronounced in diabetic coma with electrolyte imbalance. Similarly, the degree of electrocardiographic changes (flattening of the T wave and prolongation of the Q-T interval) could be correlated with the degree of the disturbance of the composition of the blood proteins.

These findings seem to indicate a causal relationship of dysproteinemia and myocardial alteration as suggested by Wuhrmann (myocardosis). The authors feel that this syndrome is a frequent complication of diabetes, particularly in diabetic coma. In its earlier stages, it is reversible and represents a faithful reflection of the degree of the metabolic disorder.

PICK

Booker, W. M., Johnson, J. B., Hayes, R. L., Thomas, R. R., Henry, W., Tureman, J. R., and Dent, F.: Effect of Cortisone on Tolerance to Ascorbic Acid and Level of Blood Cholesterol in Man. J. Clin. Endocrinol. **12:** 346, 1952.

The tolerance of 30 patients suffering from a variety of diseases to intravenously administered ascorbic acid both before and during cortisone therapy was determined. The changes in serum cholesterol during the period of the tolerance study were also determined. Normal control subjects showed an increase in plasma ascorbic acid in the first two hours following the injection of 300 mg. intravenously, whereas the patients showed a decrease in plasma ascorbic acid before treatment which was reversed toward normal by cortisone administration. The cortisone treated patients showed an increase in cell ascorbic acid even greater than the controls, in contrast to a very slight increase in cell ascorbic acid before treatment. Urinary excretion of ascorbic acid following its intravenous administration was less in the cortisone treated patients than in the same patients before treatment. Serum cholesterol levels following the administration of ascorbic acid, in the pretreatment period, remained stationary at first and then declined; whereas during cortisone therapy, there was an initial rise in serum cholesterol, followed by a fall.

Increased kidney threshold to ascorbic acid during cortisone therapy may explain the increase in ascorbic acid in the plasma concomitant with reduced excretion in the urine. The increased serum cholesterol may represent release of cholesterol from the adrenal gland as a result of increased ascorbic acid storage under the influence of cortisone.

CORTELL

PHARMACOLOGY

Schuman, C., and Simmons, H. G.: Cardiac Asthma: Its Pathogenesis and Response to Aminophylline. Ann. Int. Med. **36:** 864 (March), 1952.

The therapeutic effectiveness of intravenously administered aminophylline was observed in 75 patients who had been admitted to hospital because of paroxysmal dyspnea associated with wheezing and cough. Bronchial asthma was diagnosed in 30 and cardiac asthma in 35; the remaining 10 were considered to have both cardiac and bronchial asthma. The differentiation between bronchial and cardiac asthma was based largely on the results of circulation time studies, normal values being observed in the patients with bronchial asthma, and prolonged values being found in those with cardiac asthma secondary to left ventricular failure. The administration of intravenous aminophylline in the dosage of 0.5 Gm. in 20 cc. of saline immediately followed the circulation time determination. Of the cases of bronchial asthma, dyspnea was improved in every case, although only moderately in 4. Wheezes were altered in 11. The cardiac group was generally unimproved by aminophylline. Only 4 of these patients showed definite relief from dyspnea, and slight improvement was noted in one other case. As a further commentary on this group of 4, 2 were discovered to be asthmatic patients of long standing.

Presumably, in left ventricular failure, the respiratory distress is due to partial obstruction of bronchioles engendered by dilated vessels, secondary to acute congestion of the pulmonary vascular tree, and not to any associated bronchospasm such as exists in patients with bronchial asthma. This would serve to explain the improvement from aminophylline in the group with bronchial asthma and the lack of benefit in the patients with cardiac asthma.

WENDKOS

Marmer, M. J.: The Use of Sciatic Nerve Block for Producing Vasodilatation of the Lower Extremity and Comparative Study with Paravertebral Lumbar Sympathetic Ganglion Block. Anesthesia **13:** 207 (March), 1952.

The author performed and studied the effects of 53 nerve blocks—42 sciatic nerve blocks and 11 para-

vertebral lumbar sympathetic ganglion blocks. He concluded that a maximal degree of vasodilatation of the foot was produced by sciatic nerve block. This was not exceeded and seldom equaled by paravertebral lumbar sympathetic ganglion block.

Sciatic nerve block appears to be a better procedure than paravertebral lumbar sympathetic ganglion block because it is easier to perform, produces less discomfort, is more accurate, and no complications have been reported.

SAGALL

Hamilton, J. E., Drye, J. C., Kinnaird, D. W., and McGowan, J.: Restoration of Blood Volume in Seriously Injured Patients. Am. J. Surg. **83:** 453 (March), 1952.

A discussion is presented on the effects of depletion of blood volume in severe trauma and on methods for its restoration. Traumatic shock is due to hemorrhage with hemodilution, the gravity of the condition being in direct proportion to the amount of blood lost. However, in certain instances in which there is a selective plasma loss at the site of injury and relatively little hemorrhage, there may be hemoconcentration rather than hemodilution. Such a state is found in the case of severe burns, late cases of peritoneal soiling from lower bowel perforations, and claustridial myositis.

The immediate treatment is restoration of blood volume. If a zero blood pressure is obtained, one or two pints of low titer group "O" blood should be given in 5 to 15 minutes. In real emergency the first two pints need not be cross-matched, but all blood after the first 1000 cc. should be. When the blood pressure rises to a systolic level of 85 mm. Hg and the pulse rate drops, the patient is ready for surgery if this is indicated.

Autotransfusion should be used if possible. Fresh uncontaminated blood from the abdominal or pleural cavity should be returned to the patient. The blood is first sucked from the wound, citrated and then filtered through 10 thicknesses of gauze into a sterile Kelly bottle in preparation for intravenous administration.

The intra-arterial route for transfusion should be reserved for instances in which the intravenous method is unavailing. It will not result in pulmonary edema, while this complication not infrequently follows intravenous administration as a result of impairment in function of the left ventricle. Furthermore, much less blood is required to abolish shock when given by artery than by vein.

ABRAMSON

Howe, G. W., Ambrust, C. A., Levy, M. D., Jr., and Wagner, E. L.: Preliminary Report on the Antirheumatic Action of Heparin and Paritol-C in Gout and Rheumatoid Arthritis. Am. J. M. Sc. **223:** 258 (March), 1952.

Occasional patients under treatment with anticoagulants for myocardial infarction have manifested improvement in concomitant arthritic involvement. This observation prompted the authors to study the effects of heparin and Paritol-C on 13 patients with various rheumatic disorders, including 5 with gout, 6 with active subacute rheumatoid arthritis and 2 with acute nonspecific arthritis. Depot heparin, 200 to 300 mg. subcutaneously every 12 hours, was employed. Paritol-C was administered intravenously in doses of 3 to 4 mg. per kilogram every 12 to 24 hours. The duration of treatment depended upon the response of the patient to the drug, and the anticoagulant effects were measured by the Lee-White coagulation time, the one-stage prothrombin time and the plasma antithrombin level.

In the 5 patients with gout, a complete remission of all signs and symptoms followed the administration of anticoagulant drugs; in one case previous treatment with colchicine and salicylates had failed to control the disease. The "rebound phenomenon" which has occurred in gout following the cessation of adrenocorticotropic hormone therapy was not observed. Subjective improvement occurred in 5 of the 6 rheumatic patients; in one patient with associated pericarditis, the electrocardiogram returned to normal after Paritol therapy. The mode of antirheumatic action of these drugs is not known, but it is apparently unrelated to their anticoagulant effect according to the authors.

SHUMAN

Hussar, A. E., and Holley, H. L.: The Use of Mercurial Diuretics in the Treatment of Bromide Intoxication. Am. J. M. Sc. **223:** 262 (March), 1952

Mercurial diuretics have been demonstrated to increase the excretion of total urinary halide and, in addition, to raise the bromide-halide ratio in the urine. This feature led to the use of mercurial agents in the treatment of three patients suffering with chronic bromidism. Previous therapy for this condition inclued the use of sodium chloride, ammonium chloride, desoxycorticosterone acetate and nicotinamide. The use of the first two agents is based on the finding that chloride administration in bromidism increases the excretion of bromide by elevating the total halide excretion. Two of the patients in this report received 6 Gm. of sodium chloride daily in addition to the dietary salt, and the third was given similar amounts of ammonium chloride. The authors demonstrated that the mercurial diuretics increased the excretion of bromide both by increasing the urine volume and by increasing the bromide concentration in the urine. Rapid elimination of bromide from the body by these means was regarded as safe, effective and desirable in the treatment of bromidism, since no exacerbation of the condition was noted in these patients. It is suggested that the combined administration of sodium chloride or ammonium chloride, and mercurial diuretics is the most satisfactory treatment for bromide intoxication.

SHUMAN

Wedd, A. M., and Blair, H. A.: The Action of Acetyl-Strophanthidin on Heart Muscle. J. Pharmacol. & Exper. Therap. **104:** 334 (March), 1952.

The action of a synthetic aglycone, acetyl-strophanthidin, on the heart of the turtle and a comparison of its effects with those of digitalis are reported. With isolated spontaneously contracting auricles, the drug caused little change in rate and rhythm but did result in a decreased amplitude of contraction without muscle shortening. This effect seems to be mediated via the vagus. Digitalis drugs in contrast slow the auricular rate and increase the amplitude of its contraction. Studies of ventricular strips (spontaneously beating or rhythmically stimulated) showed early short periods of tachycardia, decreased amplitude of contraction, muscle shortening and reduced threshold for electrical stimulation. Shortening of the refractory period without impairment of contractility, a characteristic digitalis action, did not occur. It is suggested that the desirable effects of this drug reported in clinical studies of supraventricular arrhythmias may have been due entirely to its vagal action. The authors believe that unless certain concentrations of acetyl-strophanthidin will enable utilization of the vagal effects on the ventricle, the drug will not be safe for clinical practice.

SAGALL

PHYSIOLOGY

Plavcic, C.: Determination of the Velocity of Circulation by Lobeline. Acta cardiol. **6:** 999 (Fasc. 6), 1951.

The author recommends the use of Lobeline as a simple safe and objective method for determination of the rate of circulation in man and in experimental animals. The required dosage is 0.05 mg. per kilogram, injected intravenously. About 10.5 seconds following injection in normal persons, there appears a change in the rhythm of breathing (apnea and polypnea) often preceded by coughing. With the help of a pneumograph, changes of the velocity of circulation can be recorded graphically, and thus, correlated with other graphic methods used for the study of the circulation. The results obtained with Lobeline are identical with those obtained by other methods.

PICK

MacCanon, D. M., and Horvath, S. M.: Influence of Respiration on Arterial, and Right and Left Ventricular Pressures. Am. J. Physiol. **168:** 592 (March), 1952.

At the beginning of the inspiratory fall of intrathoracic pressure, the arterial and left ventricular pressures were reduced. After one or two beats, the arterial pressure began to rise and continued to do so during the remainder of inspiration. Early in expiration arterial and left ventricular pressures continued to rise, but after two or three beats this was converted to a fall which continued during the rest of expiration. Right ventricular pressures were opposite to those observed on the left. On the right both systolic and diastolic pressures fell all during inspiration, accompanied by an increase in pulse pressure. The first beat after expiration began showed a sharp rise in systolic pressure with a large increase in pulse pressure, since the diastolic pressure remained low. The second beat showed a small pulse pressure, since the systolic pressure was reduced. During the rest of expiration pressures gradually increased toward control values.

OPPENHEIMER

Ring, G. C., Navis, G. J., and Bell, L. L.: Electrokymographic Densogram as a Record of Systolic Discharge. Am. J. Physiol. **168:** 557 (March), 1952.

In the study of any electrokymographic records from the heart, careful consideration should be given to whether the records represent the true inward and outward movements of the cardiac muscle or are distorted by positional movements of the heart. Such distortions often lead to an incorrect interpretation of records. These authors point out that distortions may be diminished by placing the subject so that the positional movements of the heart are as nearly as possible parallel to the direction of the x-rays used for recording. If, in addition, the sensing element is placed over the thickest part of the cardiac silhouette, satisfactory records are obtained. The authors believe that the base to apex movement of the heart is very important in ejection of blood. This movement is not recorded by the electrokymograph.

OPPENHEIMER

Cook, S. F., Cramer, C. F., and Kenyon, K.: A Rapid Titrimetric Method for Determining the Water Content of Animal Tissues. Science **115:** 353 (March 28), 1952.

The authors describe the application in physiology and biochemistry of a relatively simple method used in industrial laboratories for the determination of the water content of liquid and solid material. This is based on the Fischer reagent and the titrimetric estimation of water. The accuracy of this method is equal to that of simultaneous determinations using the drying-to-constant-weight technic. This method is much more rapid. The water content of muscle, liver, and brain in rats was found to be 74, 72, and 79 per cent respectively.

WAIFE

RHEUMATIC FEVER

Busch, K. F. B.: Roentgen Examination in Patients with Mitral Stenosis before and after valvulotomy. Acta Radiol. **37:** 219 (March–April), 1952.

Roentgen examinations were carried out on 22 patients with mitral stenosis who were operated upon; 18 of these had valvulotomies performed. The preoperative and postoperative hearts did not vary significantly, except perhaps as pulmonary stasis was diminished after the operation. With the

methods used, the left ventricle was regarded as being enlarged in 15 of the 18 cases. The left atrium was enlarged in all cases but one, posteriorly and to the right. The left auricle (auricular appendage) appeared between the pulmonary artery and left ventricle in the postero-anterior position. The extent of pulmonary artery trunk dilatation was almost invariably underestimated when compared with the operative findings.

SCHWEDEL

Boland, E. W.: Antirheumatic Effects of Hydrocortisone (Free Alcohol), Hydrocortisone Acetate, and Cortisone (Free Alcohol) as Compared with Cortisone Acetate. Brit. M. J. **4758:** 559 (March), 1952.

Comparisons of the antirheumatic effects of hydrocortisone (free alcohol), hydrocortisone acetate, cortisone (free alcohol), and cortisone acetate given orally for short periods were made in patients with rheumatoid arthritis.

Hydrocortisone (free alcohol) was found to possess greater antirheumatic activity, milligram for milligram, than any of the other three preparations when given by mouth. By comparing the maintenance doses required for equivalent clinical control, hydrocortisone (free alcohol) was found to be approximately 50 per cent more potent than either cortisone (free alcohol) or cortisone acetate, and nearly twice as effective as hydrocortisone acetate.

The greater antirheumatic activity of hydrocortisone (free alcohol) did not seem to be accompanied by a correspondingly greater tendency to produce adverse physiologic effects.

The marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when given by mouth may be accounted for, at least in part, by differences in solubility of the compounds. The low solubility of hydrocortisone acetate may substantially lessen its alimentary absorption.

BERNSTEIN

Werkö, L., Eliasch, H., Berglund, F., and Crafoord, C.: Circulatory Studies in Mitral Stenosis before and after Commissurotomy. Ann. Surg. **135:** 290 (March), 1952.

The effect of commissurotomy on the dynamics of the pulmonary circulation was studied in five patients. In all cases cardiac output increased, while in four arteriovenous oxygen differences diminished. In four instances there was a striking reduction in pulmonary capillary and pulmonary arterial pressures. In every case there was a significant decrease in mean circulation time from the pulmonary to the brachial artery. All patients showed considerable clinical improvement.

It was pointed out that the purpose of mitral commissurotomy is to remove or diminish the obstruction to blood flow produced by the stenotic mitral valve and hence to reduce the load placed on the right heart. However, there are two factors which may prevent this aim from being achieved, namely, the existence of irreversible pulmonary vascular changes and the development of a severe degree of mitral incompetency as a result of the operation.

ABRAMSON

ROENTGENOLOGY

Rushmer, R. F., and Thal, N.: Factors Influencing Stroke Volume: A Cinefluorographic Study of Angiocardiography. Am. J. Physiol. **168:** 509 (Feb.), 1952.

These experiments represent a study of the changes in left ventricular diastolic size as related to the effective filling pressure. Heart size was recorded by cinefluorographic angiocardiography. It was demonstrated that effective filling pressure was not the most important factor determining the diastolic size of the left ventricle. Increased stroke volume may result from increased filling or from better systolic emptying, or from both of these functions operating together. Epinephrine introduced into the ventricle produced an increased filling early in the period of rapid diastolic ventricular inflow, although filling pressure was reduced. A further large inflow was demonstrated late in diastasis (presystolic). The authors consider that an increase in ventricle size without a corresponding change in effective filling pressure indicates a reduction in resistance to distension.

The following working hypothesis is invoked to explain the increase in stroke volume without an increase in effective filling pressure. Normally the change in diastolic size per unit of effective filling pressure is changed by varying amounts of epinephrine-like substance within the ventricular myocardium. Increased distensibility permits increased initial lengths (diastolic size) with unchanged or reduced venous pressure. Venous pressure is determined by ventricular distensibility in normal ranges. When the connective-tissue stroma begins to exert tension, the upper limit of diastolic volume is reached. Beyond this, increased effective venous filling pressure is required to overcome the elasticity of connective tissue. It is finally proposed that only under abnormal conditions, such as cardiac decompensation and in heart-lung preparations, is diastolic ventricular size determined by effective venous filling pressure.

OPPENHEIMER

Voris, N. C.: The Use of Serial Angiography in the Diagnosis of Space Occupying Intracranial Lesions. Am. J. Roentgenol. **67:** 360 (March), 1952.

The author presents the clinical data and describes the advantages of serial angiograms in 11 patients in whom space-occupying lesions, such as tumors, cysts and hemorrhage, were considered. Anteroposterior as well as lateral films are necessary

The most dependable sign is the displacement of blood vessels. Diminution in arterial supply or in the venous drainage occurs fairly frequently with highly vascular intracranial neoplasms.

SCHWEDEL

Pacheco, C. R., and del Castillo, H.: Angiographic Studies after Pulmonary Resection. J. Thoracic Surg. **23:** 262 (March), 1952.

In 13 cases of pulmonary resection (lobectomy or pneumonectomy), the authors studied the remaining pulmonary bed by means of angiography. It was found that the pulmonary artery and mediastinum were displaced toward the operated side unless thoracoplasty or filling of the cavity with plastic material was carried out. This displacement was more marked the longer the time between the operation and the angiographic study.

It was concluded that allowing the rest of the lobes or the other lung to re-expand and fill the cavity left after lobectomy or pneumonectomy gives rise to a state of respiratory insufficiency. Hence a collapse method should be substituted for the extirpated lung tissue to prevent the overexpansion of the remaining pulmonary tissue.

ABRAMSON

Mannheimer, E., Landtman, B., and Melin, K. A.: Complications of Angiocardiography and Cardiac Catheterization. Cardiologia **19:** 337 (Fasc. 6), 1951.

The authors discuss possible hazards and complications encountered in connection with angiocardiography and cardiac catheterization. Both venous and arterial angiocardiography may be followed by cerebral complications, since contrast material, injected under pressure, may enter the cerebral circulation. Electroencephalograms were recorded in 45 instances before and following the procedure. Transient alterations were found in about 10 per cent of the cases without venus-arterial shunt; changes persisting for more than 48 hours were present in more than 20 per cent of the cases with an overriding aorta and in about 50 per cent of the cases submitted to arterial angiography. One cyanotic case in heart failure died within five minutes following intravenous injection of the contrast-material. A second fatality occurred in a 13 year old girl with coarctation, when aortography was repeated at an interval of 45 minutes. In view of these experiences the authors feel that angiocardiography should be employed only if a diagnosis cannot be established by simpler methods, and then performed with all necessary precautions, and never repeated in the same session.

Although complications may occur during cardiac catheterization, this method appears less dangerous than angiocardiography. Among 220 catheterizations performed, there was no fatality. More serious accidents were periods of anoxia in cases of tetralogy due to occlusion of the stenotic ostium of the pulmonary artery by the catheter. Arrhythmias, which usually appear with the catheter in the infundibular region, may be due to formation of ectopic beats or to disturbances of AV conduction; they are transient and mostly without clinical significance. Difficulties may arise when the catheter cannot be proceeded into the right ventricular cavity, due to venous spasm or if it enters the coronary sinus or a vein with anomalous drainage. Possible fallacies of pressure determinations and of gaseous analysis in such instances are pointed out.

PICK

Petersen, G. F.: Atherosclerosis of the Abdominal Aorta. A Roentgenologic Study. Acta Radiol. **37:** 356 (March–April), 1952.

Roentgenograms in the left posterior oblique position are advocated to visualize calcification in the lower abdominal aorta and in the common iliac arteries. In a series of 220 cases thus examined, the incidence of calcification in females was more than twice that of males (48.5 per cent as against 20.2 per cent). Calcification was present in 71 per cent of 73 hypertensive patients, and only in 34 per cent of nonhypertensive patients. This suggests that correlation of calcification and coronary arteriosclerosis is high.

SCHWEDEL

Bass, H., Greenberg, D., Singer, E., and Miller, H.: Pulmonary Changes in Uremia. J. A. M. A. **148:** 724 (March 1), 1952.

This report concerns the lung changes in eight fatal cases of uremia. Roentgen changes were those of extensive inner lung zone densities. Such changes were transient in some cases where alleviation of left ventricular failure resulted in a disappearance of lesions. Physical findings in most cases were minimal. Dyspnea ranged from mild to severe. Pathologic changes were typical of those found in many conditions brought on by altered capillary fragility and were most marked in cases with glomerulonephritis. It is felt that these uremic pulmonary alterations occur more frequently than is generally known. The recognition of "uremic lungs" is important from the standpoint of prognosis and its resemblance to other pulmonary diseases.

KITCHELL

Sutton, G. C., Wendel, G., Wedell, H. G., and Sutton, D. C.: Evaluation of Intracardiac Angiocardiography. Am. J. Roentgenol. **67:** 596 (April), 1952.

The conventional peripheral angiocardiography, wherein the opacifying substance is injected into an arm vein, is differentiated from intracardiac angiocardiography, where the injection is made through a catheter inserted into the right external jugular vein. The 10–14F catheter is directed into the right ventricle or into the pulmonary artery, and the same amount of opaque substance (50 cc. of the 70

per cent solution) is injected as in the peripheral arm vein method. Circulation time is determined with a 50 cc. volume for greater accuracy when only two or three films are to be taken rapidly in succession. Repeat angiocardiography may be done in the P-A or oblique positions in 15 minutes.

The authors compare 36 cases performed with this method to a series of 47 cases with peripheral injection of the dye and conclude that, although the method is slightly more complicated and time consuming, the advantages of better opacification, better positioning, and better diagnostic films of the left heart and aorta justify the procedure.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Swan, H., Forsee, J. H., and Goyetti, E. M.: Foreign Bodies in the Heart. Indications for and Technic of Removal with Temporary Interruption of Cardiac Blood Flow. Ann. Surg. **135:** 314 (March), 1952.

The authors evaluated the various factors which determined whether surgical removal of foreign bodies in the heart was indicated. The most important point was the presence of persistent or recurrent sepsis, as manifested by fever, leukocytosis, positive blood cultures, or septic or bland emboli. Another condition in favor of surgical intervention was the identification of the foreign body, either lying free in a chamber of the heart, impinging upon a valve leaflet, or impinging upon the myocardium during cardiac systole. To diagnose with great accuracy the exact location of the foreign body, it was necessary to resort to angiocardiography. Contraindications to elective surgery were small foreign bodies, location of the body entirely within the myocardium, and absence of symptoms.

In the case of the authors' two patients, the foreign bodies were in the interventricular septum. These were removed surgically; but before this was performed a relatively dry field for intracardiac manipulation was obtained by temporarily occluding the venae cavae.

ABRAMSON

de Takats, G., and Marshall, M. R.: Surgical Treatment of Arteriosclerotic Aneurysms of the Abdominal Aorta. Arch. Surg. **64:** 307 (March), 1952.

The authors reviewed the literature regarding the various methods of treating abdominal arteriosclerotic aneurysms and also discussed the results obtained in their series of 10 cases. In seven of the latter a cellophane collar alone or in conjunction with the use of talcum or quartz dust was utilized, while in two either wiring was done or this was performed at the same time that a cellophane collar was applied. In the remaining case a cutis graft was placed around the sac.

It was found that the cellophane collar produced little effect. However, the addition of irritant talcum powder caused a definite improvement in the clinical course. Cellophane containing dicetylphosphate was considered to be more effective than the plain material.

ABRAMSON

Beattie, E. J., Jr., and Greer, D.: Laceration of the Aorta. Case Report of Successful Repair Forty-eight Hours after Injury. J. Thoracic Surg. **23:** 29[illegible] (March), 1952.

The authors presented a case of a laceration of the ascending aorta in a young male. Operation was performed 48 hours after the injury. A knife blade 6 cm. long was removed from the anterior mediastinum, and a laceration of the aorta inside the pericardium was successfully closed. The postoperative course was uneventful.

ABRAMSON

Reid, L. C., Stephenson, H. E., Jr., and Hinton, J. W.: Cardiac arrest. Arch. Surg. **64:** 409 (April), 1952.

The authors review the pathogenesis of cardiac arrest and means to prevent it. Anesthetic agents appear to depress the automaticity of the specific conduction tissue, since they cause the heart to become more vulnerable to vagal stimulation. Anoxia, while not having a direct role, may potentiate the action of the anesthetic. As a result, there is a further decrease in the capacity of the specific tissue to form impulses.

Since undesirable reflexes may originate in the mucosa of the respiratory or gastrointestinal tracts, the introduction of various mechanical contrivances into the trachea or esophagus is not without danger. Likewise, clamping or tying structures containing vagal nerve endings may cause depression of specific tissue in the heart. Therefore all such contemplated procedures should be covered by the previous use of atropine.

ABRAMSON

VASCULAR DISEASE

Lyon, T. P., Jones, H. B., Graham, D. M., Gofman, J. W., Lindgren, F. T., and Yankley, A.: Further Studies on the Relationship of S_f 10-20 Lipoprotein Molecules to Atherosclerosis. Arch. Int. Med. **89:** 421 (March), 1952.

The class of lipoproteins in human blood designated as the "S_f 10–20 class," which has previously been reported to be associated with atherosclerosis, has been studied in a large group of patients with coronary artery disease over a one to one and one-half year period. Recurrence of myocardial infarction in patients with previous infarcts, and occurrence of infarction in patients with angina pectoris developed predominantly in that part of the group showing the highest S_f 10–20 concentrations over the period of observation.

Low-fat, low-cholesterol dietary management of patients with coronary artery disease was effective in reducing average S_f 10–20 levels. This reduction in S_f 10–20 levels was associated with a marked reduction in rate of occurrence of new myocardial infarctions in the group. Heparin suppressed the rise in concentration of S_f 10–50 molecules in the cholesterol-fed rabbit and minimized the development of atherosclerosis. Heparin produced similar alterations in the lipoproteins of the human subject. Clinically, administration of 20 to 100 mg. of heparin produced dramatic relief of angina pectoris in 30 of 32 patients for periods of 3 to 10 days following a single injection.

BERNSTEIN

Wartman, W. B.: New Aspects of the Pathology of Arteriosclerosis. Northwestern Univ. Bull. Med. School **26:** 5 (Spring), 1952.

This review presents some of the factors other than disturbance of lipid metabolism which may be important in the cause and development of arteriosclerosis. Arteriosclerosis is a pathologic lesion which may be caused by numerous etiologic agents, many of which are well known. The significance of early changes in the media of the artery, the possibility that tissue factors may determine the site of deposition of cholesterol in the arterial wall, and the evidence that some forms of arteriosclerosis may result from organization of thrombi are discussed. Consideration has also been given to the fact that bleeding into the diseased intima may be responsible for many of the clinical complications of arteriosclerosis, such as occlusion, ischemia and extravascular hemorrhage.

BERNSTEIN

Williams, M. H.: Traumatic Arteriovenous Aneurysm Associated with Streptococcic Septicemia. J. A. M. A. **148:** 726 (March 1), 1952.

The author reports the tenth case of traumatic arteriovenous aneurysm associated with septicemia and states that this is the sixth case in which cure has followed operation. The lesion was in the left infraclavicular area and followed a stab wound which occurred 15 years previously. After an illness of 3 months, the patient was hospitalized for study and blood cultures showed a heavy growth of hemolytic streptococci. Antibiotic therapy was begun on the day of admission, and a total dose of 900,000 units of penicillin was given for 16 days, after which the dose was reduced to 400,000 units daily. Recovery followed lateral suture of the aneurysm without actual removal of the source of infection.

KITCHELL

McCook, W. W.: Arteriovenous Fistula of the Aortic Arch. J. Thoracic Surg. **23:** 299 (March), 1952.

The author reported a case of traumatic arteriovenous fistula between the aortic arch and the left innominate vein following a stab wound. At the time of operation, which was performed 17 days after the injury, a pulsating mass about 8 cm. in diameter was found in the retrosternal space. This was dissected free, and the aneurysm was opened and emptied after the communications between it and the aorta and the innominate vein were occluded. Then the sac was excised, the aortic communication closed and the innominate vein ligated. No postoperative difficulties were encountered except for a temporary febrile reaction.

ABRAMSON

Gardner, C.: Traumatic Vasospasm and Its Complications. Am. J. Surg. **83:** 468 (March), 1952.

The author presented six cases of traumatic vasospasm to support the view that this state was not always innocuous; but depending upon its severity and duration, it could produce Volkmann's contracture, necrosis of the muscles or even gangrene of the entire limb. Various therapies were attempted on the patients, but none was found to be effective.

ABRAMSON

Wilkins, R. W., Mixter, G., Jr., Stanton, J. R., and Letter, J.: Elastic Stockings in the Prevention of Pulmonary Embolism: A Preliminary Report. New England J. Med. **246:** 360 (March 6), 1952.

This study is a preliminary report concerning the experience with 5,426 consecutively available hospitalized patients, half of whom were assigned by chance to wear elastic stockings and the other half to wear loosely applied nonelastic stockinette. Earlier studies had shown that the linear velocity of blood flow in the leg veins was accelerated by local compression. Because of the belief that acceleration of flow would tend to decrease the likelihood of thrombosis in the calf veins, it was decided to try elastic compression of the legs as a prophylactic measure against phlebothrombosis and pulmonary embolism in hospitalized patients. Subsequent postmortem and clinical analyses indicated that fatal pulmonary embolism was less frequent in the stocking group than in the controls, but that thrombotic disease without pulmonary embolism was equally common in the two groups.

Knee-length stockings providing pressures up to 10 to 15 mm. Hg were found to be most satisfactory. The chief contraindication to the elastic-stocking prophylaxis was the presence of ischemic vascular disease in the legs. Ulceration, local inflammation or trauma of the legs were other contraindications. Patients with massive edema of the legs were also excluded because of the fear of producing pulmonary edema; but since the incidence of pulmonary embolism in such patients was very high, the extension of the study which is being carried out currently will include this group also. The experience in this study confirmed earlier reports that thromboembolic disease occurs especially in those patients who are elderly, who have congestive heart failure

or who have undergone major abdominal operations, especially for neoplastic disease.

ROSENBAUM

Lambert, J., and Grenade, A.: False Spontaneous Aneurysm of the Deep Femoral Artery in a Patient with Aortic Regurgitation. Acta cardiol. **7:** 421 (Fasc. 4), 1952.

A case is reported of 43 year old man with aortic insufficiency who developed typical clinical signs of an aneurysm of the thigh, most likely due to spontaneous rupture of the deep femoral artery. The diagnosis was confirmed by angiography and at surgery. The latter revealed a lateral perforation of the deep femoral artery leading into a pulsating aneurysmatic sac filled with blood clots. The lesion could be repaired without difficulty.

Spontaneous rupture of a large artery is rare and the authors discuss possible etiologic factors. As most likely etiology in the presented case they consider a local weakening of the arterial wall due to previous bacterial or rheumatic arteritis which eventually gave in to the elevated blood pressure in the lower extermities associated with the aortic lesion. The hypertension might, in addition, have produced atheroma of the vessel wall and thus, was probably responsible for its partial rupture and the subsequent formation of an aneurysm.

PICK

Michelazzi, A. M.: Acute Cerebral and Coronary Circulatory Disturbances. Cuore e Circolaz. **36:** 93 (April), 1952.

Forty clinical cases are discussed. The double symptomatology, cerebral and cardiac, is explained in the following way: (1) In some cases, a sudden circulatory collapse caused by myocardial infarction led to cerebral damage. This consisted of (a) cerebral thrombosis, (b) minute cerebral hemorrhages, and (c) diffuse psychic disturbances caused by anoxemia. Late disturbances were also observed. (2) In other patients, detachment of a mural thrombus caused cerebral embolism. (3) In some cases, an initial hypertensive reaction consequent to coronary occlusion was followed by small cerebral hemorrhages. (4) In other cases, the simultaneous onset of coronary and cerebral occlusions was explained by an initial cerebral lesion which precipitated the coronary damage, probably through a sudden change of blood pressure.

LUISADA

Crane, C.: Deep Venous Thrombosis in the Leg Following Effort or Strain. New England J. Med. **246:** 529 (April 3), 1952.

Thirteen cases of venous thrombosis of the leg are reported, in each instance the condition following uncomplicated effort or strain. The disorder occurs predominantly in males and is generally unilateral at the outset. Pulmonary embolism is rare. It is believed that at least two etiologic factors are involved in the production of this entity. The first is an increase in intra-abdominal pressure resulting from fixation of the diaphragm and contraction of the abdominal musculature, which occurs during voluntary straining, lifting, or jumping. As a consequence, there is a rise in venous pressure in the inferior vena cava, the iliac veins, and then the iliofemoral veins. Any local weak point in the venous system, such as the foramen ovale, is thus exposed to a bursting force. The second etiologic factor is muscular contraction in the limb. In most situations of effort, the large flat muscles of the calf and the quadriceps group of the thigh contract simultaneously, thus compressing sharply the great veins of the calf against the posterior tibial wall. This causes venous blood to be pumped forcibly through the relaxed muscular compartment surrounding Hunter's canal. Violent or repeated muscular contraction, when added to the high venous pressure factor, may also contuse the thin-walled vein, bruise the vasa vasorum, or, in association with a muscle tear, rupture a venous branch at its point of origin.

It is necessary to differentiate deep venous thrombosis from symptoms and signs of a muscle strain. In the case of the latter the stiffness, pain, and disability are due to hematoma formation, the severity of the complaints approaching a peak in 4 to 24 hours. If any edema is present, it appears in a matter of a few hours and is local. The stiffness, pain, disability, and swelling of a venous thrombosis follow the gradual establishment of a sufficient degree of venous blockade, which generally requires from two to seven days.

ABRAMSON

Logue, R. B., and Sikes, C.: A New Sign in Dissecting Aneurysm of Aorta. J. A. M. A. **148:** 1209 (April 5), 1952.

A brief clinical summary of dissecting aneurysm of the aorta is presented, and a new sign—pulsation of the sternoclavicular joint—is described. The authors feel that this sign does not occur in entities that present confusion in differential diagnosis. It is not seen with the chronic aortic enlargement occurring in hypertension or syphilitic aortic insufficiency. They feel the presence of a pulsating sternoclavicular joint with aortic insufficiency, hypertension, and a dilated aorta is diagnostic of dissecting aneurysm. Pulsating sternoclavicular joints are described in the following conditions other than dissecting aneurysm: (1) syphilitic aneurysm of the innominate, carotid, or subclavian arteries; (2) partial rupture of saccular aneurysm of the arch of the aorta; and (3) persistent right aortic arch in which the right aortic arch normally extends more cephalad than the left arch. Five cases are reported illustrating the importance of the new sign in the differential diagnosis of chest pain.

KITCHELL

Gordon, C. A., Rosenthal, A. H., and O'Leary, J. L.: Venous Thrombosis and Pulmonary Embolism. Am. J. Surg. **83:** 556 (April), 1952.

The authors present 11 case reports of venous thrombosis and pulmonary embolism associated with pregnancy, and discuss the various points regarding diagnosis and treatment brought out in the clinical histories. Attention is called to the fact that thrombosis may be primary in the veins of the thigh and pelvis as well as in the deep veins of the calf. Pulmonary embolism may arise from either of these sites, and it may occur repeatedly. With regard to treatment, paravertebral block is not indicated unless signs of vasospasm are prominent. Anticoagulant therapy is not recommended for antepartum use. After delivery heparin can be administered without much fear of bleeding from the placental site. Concerning surgical procedures, the authors are of the opinion that ligation of the femoral veins is not sound. Ligation of the inferior vena cava, however, has much more in its favor as a means of preventing pulmonary embolism.

ABRAMSON

Lippmann, H. I.: Intra-arterial Priscoline Therapy for Peripheral Vascular Disturbances. Angiology **3:** 69 (April), 1952.

Seventy-six patients with peripheral vascular disease were treated with intra-arterial priscoline. When possible, a dose was selected which produced no systemic response. Although treatment schedules varied widely, the majority of patients received two to three daily injections for 3 to 10 days, one to two daily injections for the following seven days and one injection daily for several weeks. One or two injections weekly eventually sufficed to produce continuous vasodilation. The most significant effects of therapy were observed in the favorable response of ischemic lesions of the heel. Other conditions also improved by intra-arterial Priscoline were the following: ischemic lesions of the extremities other than the heel, acute deep thrombophlebitis with arterial spasm, and intractable Raynaud's attacks. No permanent damage to the injected arteries was observed.

WESSLER

Martorell, F.: Dicumarol: Dangerous and Rather Ineffective Drug. Angiology **3:** 185 (April), 1952.

The author believes that Dicumarol is a dangerous and relatively ineffective anticoagulant when compared with heparin. Although Dicumarol can be given orally and is inexpensive, it is a poison which acts by preventing the formation of prothrombin in the liver, it has a delayed and prolonged action, it requires careful laboratory control, and it may lead to fatal hemorrhage. From clinical observations and experimental studies in rabbits, the therapeutic and toxic doses have been found to be too close for safe and effective clinical use.

WESSLER

OTHER SUBJECTS

Johnson, D. A., Roth, G. M., and Craig, W. McK.: Orthostatic Hypotension following Chordotomy for Intractable Pain. Proc. Staff Meet. Mayo Clin. **27:** 131 (March), 1952.

Orthostatic hypotension may occur as a complication of bilateral high thoracic section of the anterolateral quadrants of the spinal cord. It is likely that some of the cases of idiopathic orthostatic hypotension result from lesions in the spinal cord at this level, since anhydrosis is common in these cases and the patients may recover. The greater part of the efferent autonomic fibers do not seem to be intimately associated with the pyramidal tract in the cord.

SIMON

Friedman, M., Byers, S. O., and Rosenman, R. H.: The Accumulation of Serum Cholate and Its Relationship to Hypercholesteremia. Science **115:** 313 (March 21), 1952.

The authors had obtained evidence that hypercholesteremia appears to be secondary to hypercholatemia. The present study investigated the relationship between hypercholatemia and blood cholesterol levels. Among 25 normal subjects, the mean serum cholesterol was 228 mg. per 100 ml. and serum cholate was 5.3 mg. per 100 ml., with a cholesterol–cholate ratio of 43. Values of hypercholesteremic subjects with such clinical disorders as nephrosis, xanthoma, diabetes, myocardial infarction, and hypothyroidism, revealed an elevated serum cholate, with a fall in the cholesterol–cholate ratio.

Hypercholesteremia was invariably associated with an elevation of serum cholate. The elevated cholate level appears irrespective of the different etiologies of hypercholesteremia, and the degree of hypercholesteremia bore a close relationship to the extent of hypercholatemia.

Clinical hypercholesteremia may be secondary to an initial derangement of cholate metabolism, and the role of the liver must be kept in mind in evaluating factors involved in human hypercholesteremia.

WAIFE

Walker, S. H.: Cardiac Complications of Pertussis. J. Pediat. **40:** 200 (Feb.), 1952.

One hundred and fifty-nine cases of pertussis were studied in a six month period; three, or 1.9 per cent, of these cases developed manifestations of myocardial insufficiency. There was no evidence of the previous existence of cardiac or respiratory disease prior to the onset of pertussis. Myocardial involvement was suggested by persistent and excessive tachycardia, moderate enlargement of the liver, poor quality of the heart sounds, and dyspnea and orthopnea out of proportion to the severity of the pulmonary disease. It seems probable that in these cases myocardial insufficiency was secondary to

some factor which appeared during the course of the pertussis. One patient died in cardiac failure; one had failure of several weeks' duration, which then disappeared; and one developed minimal signs of myocardial insufficiency without frank failure. A myocarditis directly attributed to *H. pertussis* has never been reported.

There was no evidence of myocarditis in the one autopsied case. The diagnosis of myocarditis, as the cause of myocardial insufficiency, could not be established. There was venous pressure elevation and hepatic enlargement, which could be consistent with right ventricular insufficiency. A frequent complication of pertussis, in the experience of the authors, has been evidence of pulmonary interstitial emphysema, hyperexpansion of the chest, dyspnea and depression of the diaphragm with apparent enlargement of the liver and spleen. Each of the cases of myocardial insufficiency was associated with this condition. It is, therefore, difficult to distinguish the early manifestations of cardiac failure from the pre-existing pulmonary state. However, this may cause an increase in the peripheral resistance in the pulmonary circuit, which could conceivably produce a sufficient increase in right intraventricular residual blood to extend the fibers beyond their critical length.

The authors conclude that the clinical manifestations of myocardial insufficiency seen during the course of pertussis are associated with the manifestations of pulmonary interstitial emphysema and may be consequent to the right ventricular stress occasioned by this condition.

MARGOLIES

Adlersberg, D., Schaefer, L. E., and Drachman, S. R.: The Incidence of Hereditary Hypercholesteremia. J. Lab. & Clin. Med. **39:** 237 (Feb.), 1952.

A study of the families of 200 consecutive unselected admissions, 100 men and 100 women, to the medical wards of a large general hospital revealed an incidence of hereditary hypercholesteremia of 5.5 per cent. Hereditary hypercholesteremia was considered present when three or more immediate members of a family were found to have a total serum cholesterol level in excess of 280 mg. per 100 ml. as determined by the Sperry-Schoenheimer method.

The serum cholesterol levels of these index patients were elevated or depressed in many instances by their disease. Consequently, in patients with conditions which are commonly associated with hypercholesteremia, it was impossible to determine whether a normal or elevated serum cholesterol level was present prior to the onset of the disease. Pyrexia, especially when high or of long duration, and diseases producing cachexia are known to lower the total serum cholesterol level. Under such conditions, idiopathic hypercholesteremia might have been masked, since it was often impossible to perform serum cholesterol determinations after the patient's recovery.

The population of this hospital is not truly representative of New York City, the site of the study. In a wider, more important sense, the population of the hospital is not a representation of the population of the United States, since racial origins and environmental factors (climate, diet, occupation etc.) differ significantly from those of other areas. It would be of great value, therefore, to assay population groups in other parts of the country in order to obtain a more accurate estimate of the incidence of hereditary hypercholesteremia.

There was a high incidence of hereditary hypercholesteremia among the patients of Jewish descent. In 104 Jewish families, there were 11 instances of proved hereditary hypercholesteremia (10.6 per cent), whereas in 96 non-Jewish families, this abnormality was encountered in only one instance (1 per cent).

This survey represents the first attempt to estimate the occurrence of hereditary hypercholesteremia in the population. In view of the possible relationship between hypercholesteremia and atherosclerosis, which is more frequently observed in a progressively aging population, these genetic studies assume an added significance.

MINTZ

Pederson, A., and Husby, J.: Venous Pressure Measurement. II. A New Technique for Direct Venous Pressure Measurement Using an Electric Condenser Manometer. Acta med. scandinav. **141:** 317 (March), 1952.

The authors used the Tybjaerg Hansen electric condenser manometer which is an elaboration of the apparatus designed by Buchthal and Warburg for measurement of the venous pressure. Using small caliber needles, the manometer is said to constitute a practically rigid system with a sufficiently high natural frequency and suitable degree of damping that pressure fluctuations occurring in the circulation are recorded with virtually no distortion in phase or amplitude. Pressure measurements may be recorded continuously for several hours, if desired.

The study of various basal conditions suggested that the venous pressure, measured from the reference level, is the same whether the arm is at the zero point or below this level, for example, resting on the table. Abduction of the arm to 45 degrees is recommended. Compression of venous pathways proximal to the site of puncture increases the venous pressure recorded, whereas increased resistance to flow distal to the site of venipuncture causes a decrease in the pressure recorded. Patients should be lying flat when measurements are made. Measurements of the venous pressure in 40 normal adults disclosed a range between 70 and 106 mm. of water

with an average of 88 mm. Fairly good agreement with simultaneous pressure measurement employing a blood-filled glass tube was observed in the majority of 38 cases studied.

ROSENBAUM

Villebrands, A. F., Groen, J., and Frenkel, M.: A Metabolic Study of the Disturbances Taking Place during Diabetic Coma and its Treatment, with Special Reference to the Changes in Potassium Metabolism. Acta med. scandinav. **141:** 331 (March), 1952

This report is concerned with detailed studies made in five patients with diabetic coma. The serum sodium and chloride levels were practically normal during coma and remained so during treatment. It is emphasized, however, that in view of the evidence of dehydration, these normal concentrations do not indicate a normal state of water and salt in the extracellular space. The serum potassium level was elevated in cases of severe diabetic coma and dropped well below the normal level during treatment, the lowest levels of 2.5 to 3.0 mEq. per liter being reached in one to three days. These low potassium levels persisted even when large amounts of potassium were given in the diet. During coma, the urinary excretion of potassium was high; it fell rapidly during treatment and remained so for several days despite oral administration of large amounts of potassium with food or as potassium chloride. This positive potassium balance in the presence of a decreased serum potassium is interpreted as due to a shift of potassium from the extracellular to the intracellular space. Signs of potassium depletion did not appear in any of the cases reported here, probably because the potassium level did not drop low enough. Nitrogen excretion in the urine was high during coma but fell rapidly during treatment, and nitrogen balance was restored rapidly when nitrogen was furnished in the food. Phosphate metabolism was found to follow a pattern resembling that of potassium except that only slight phosphorus retention occurred and the phosphate balance was restored more promptly.

The authors feel that since the decrease in serum potassium during treatment is only infrequently great enough to produce clinical signs, the intravenous administration of potassium with the accompanying risks of cardiac arrhythmias is in general undesirable It is considered advisable to give liberal amounts of foods containing potassium as soon as the patient's condition permits.

ROSENBAUM

Lyon, E.: Modern Viewpoints on Cardiovascular Disturbances in Influenza. Israel M. J. **11:** 25 (Feb.–March), 1952.

The etiologic agent of influenza is today recognized as a virus; but a mixed nature of the influenzal infection, for example, virus plus bacteria, is frequent. The influenzal infection may cause cardiovascular disturbances of which we know the following: (1) myocarditis, fatal cases of which are rare, while mild, reversible cases are more frequent; (2) Q-T prolongation of the electrocardiogram as a sign of impairment of the functional integrity of the myocardium; and (3) acute neurocirculatory asthenia, a disorder of the autonomous nervous system.

These cardiovascular disturbances may occur alone or in combination with each other. The importance of complete bed rest in myocarditis is stressed.

BERNSTEIN

Hopkins, R. W.: Studies in the Arctic With the Flicker-Fusion Nitroglycerin Test. A New Method of Evalutaing Cardiovascular Status. New England J. Med. **246:** 401 (March 13), 1952.

This report is concerned with the results of 114 flicker-fusion nitroglycerin tests performed on 81 subjects in the Arctic during a period when the temperature ranged from a daily average of −15 F. in the spring to +45 F. in the summer. The subjects were living in camp conditions which required them to be outdoors much of the time. None of the subjects had clinical evidence of cardiovascular disease. The technic of Krasno and Ivy was employed. Thirty-eight per cent of the patients showed abnormal responses. This high proportion of abnormal responses was attributed to the low environmental temperatures. When the average daily temperature was 33 F. or above only 18 per cent abnormal responses occurred; but when the temperature was 32 F. or below, 50 per cent abnormal responses were recorded. Of 16 subjects who had abnormal responses during cold weather, 13 became normal when reexamined during the summer. The abnormal responses occurred almost as commonly in subjects who had been indoors for two or three hours as in others who were tested immediately after coming indoors.

The author concludes that the subjects showing abnormal responses presumably had some degree of subclinical hypertonus, even though showing no clinical evidence of vascular impairment. It is suggested from these studies that exposure to abnormal environment must be considered when the flicker-fusion nitroglycerin test is used in clinical evaluation.

ROSENBAUM

Pordy, L., Master, A. M., and Chesky, K.: Value of Cardiac Function Tests in Industry. J.A.M.A. **148:** 813 (March 8), 1952.

The necessity for dependable cardiac function tests especially in industry is demonstrated by the large number of patients with heart disease in whom the routine clinical studies are all normal. In industry as in clinical practice, a battery of clinical function tests should be employed routinely and

regularly for the early detection of pathologic cardiac states and for the accurate evaluation of heart function. The authors discuss the "two-step" exercise electrocardiogram test and state that the diagnosis of coronary insufficiency is practically, but not absolutely, excluded if both the single and double "two-step" tests are normal. An abnormal single or double "two-step" test is objective evidence of coronary insufficiency. It is felt that the anoxemia test is hazardous, and its yield of abnormal cases in cardiac patients is relatively small. Ballistocardiography, by the simple Dock technic, is described as a valuable supplement to electrocardiography and to exercise tests in the cardiac diagnostic armamentarium. It is too early to evaluate properly the Krasno-Ivy nitroglycerin flicker test, but further study of it is definitely warranted.

KITCHELL

Gorlin, R., and Dexter, L.: Hydraulic Formula For the Calculation of the Cross-Sectional Area of the Mitral Valve During Regurgitation. Am. Heart J. **43:** 188 (Feb.), 1952.

The authors have applied standard hydraulic principles to determine some quantitative aspects of mitral valvular regurgitation. In addition to pressure and flow data obtained by cardiac catheterization, it was necessary to know the forward area of the mitral valve in order to calculate the mitral regurgitant flow and area. This was measured either at autopsy or by digital palpation at the time of surgery. The authors point out that only rough conclusions may be drawn about the size of the regurgitant orifice or about the relationship between the regurgitant and forward valve areas, because the former is only a gross approximation of the true area, while the latter is actually measured anatomically. Even without accurate area measurements, the authors state that the calculations may be used to describe the circulatory dynamics of mitral regurgitation, to evaluate regurgitation before and after mitral surgery, to elicit some of the functional and anatomic characteristics of the regurgitant orifice, and to plan in the surgical relief of mitral regurgitation.

HELLERSTEIN

Weisenfeld, S., and Messinger, W. J.: Cardiac Involvement in Progressive Muscular Dystrophy. Am. Heart J. **43:** 170 (Feb.), 1952.

A study was made of 44 cases of progressive muscular dystrophy, ranging in age from 13 to 77 years. Eighty-five per cent of the patients had some clinical manifestation of dysfunction of the cardiovascular system, and 80 per cent had abnormalities of the electrocardiogram. The most common abnormality was tachycardia, occurring in 50 per cent of the patients. Seven patients had tachycardia in the form of paroxysms. In 13 of the 18 patients with complete precordial records, the R wave was tall in V_1 and V_2. Abnormal P waves were common. In one autopsied case, the auricular musculature was examined and found to be involved by the dystrophic process. Histologic examination of the heart uniformly revealed an increase in connective tissue which, by special stain, in some instances involved nerve endings. Muscle cells were atrophic, and fatty replacement was common, especially in the right ventricle. Loss of striations of muscle cells, and hypertrophy and swelling were noted. The lesions in the heart were similar to those found in the pectoral muscles, diaphragms, stomach, and rectum. Significant coronary artery disease was not present. The clinical entity of dystrophic heart disease is now well established and should be suspected in patients with progressive muscular dystrophy and unusual electrocardiograms.

HELLERSTEIN

Weisberger, A. S., Meacham, G. C., and Heinle, R. W.: Simple Method for Demonstrating the "L.E." Phenomenon in Peripheral Blood. J. Lab. & Clin. Med. **39:** 480 (March), 1952.

The demonstration of leukocytic inclusion bodies ("L.E." cells) and rosettes in bone marrow or peripheral blood has been helpful in the diagnosis of acute disseminated lupus erythematosis. A simple procedure has been devised for the excellent separation of leukocytes by accelerating the erythrocyte sedimentation with the use of fibrinogen. Films prepared by this technic are composed almost entirely of large members of leukocytes and platelets, so that the finding of "L.E." cells is greatly facilitated even if the patient has a severe leukopenia. Only a small number of erythrocytes are present. The results with this method appear to be entirely comparable to those obtained when the bone marrow content placed in plasma from the patient is used as a source of leukocytes.

MINTZ

BOOK REVIEWS

Clinical Heart Disease. Fourth Edition. *Samuel A. Levine.* Philadelphia, W. B. Saunders, 1951. 556 pages, 192 figures. $7.75.

In the preface to the first edition of *Clinical Heart Disease,* published in 1936, Dr. Levine expressed his preference for teaching that which is practical and useful in medicine in order to provide the practicing physician with information that is directly helpful in the care of the patient. In this the fourth edition he has kept firmly to this purpose. In the interval some forms of acquired heart disease, including bacterial endocarditis and valvular disease, have become more or less amenable to treatment. In those days recovery from bacterial endocarditis was a curiosity and the surgical treatment of acquired valvular disease, which Dr. Levine had helped to initiate, had been abandoned because of discouraging failures. With the advances in knowledge of the cause, diagnosis and the relief of cardiac disease, which the progress of these years has provided, Dr. Levine has kept steadily in step and, with his special genius as a teacher, he has set down his experience and his principles in this very useful volume.

No one who knows Dr. Levine will deny that he has definite ideas of his own. With some of these ideas one may express reserved disagreement but one cannot avoid admiration for the mass of knowledge here described. The volume has won a firm place among the practical tools of the modern cardiologist.

E. Cowles Andrus

The Approach to Cardiology. *J. Crighton Bramwell, with a Foreword by A. V. Hill.* New York, Oxford University Press, 1951. 122 pages, 66 figures. $3.75.

The purpose of this book is to direct the transition of the medical student from basic laboratory procedures to the clinical study of physiology and pharmacologic problems in the living subject. The book contains most of the basic, orthodox physiologic aspects of the cardiovascular system related to detailed symptomatology and clinical entities. Abnormalities of function and the symptoms and signs of organic disease are properly differentiated. Great care is taken to integrate the symptoms and signs of cardiovascular disease with all other aspects of clinical medicine. The book, when carefully read, will give a basic understanding of cardiovascular problems.

G. C. Griffith

Disorders of the Heart and Circulation. *Edited by Robert L. Levy.* New York, Thomas Nelson & Sons, 1951. 944 pages, 370 illustrations, 61 tables. 6 charts. $12.00.

This book is composed of a series of articles prepared originally for the Nelson Loose-Leaf System of Medicine. The editor indicates in his preface that the decision to publish a separate monograph was made only after the manuscripts had been submitted. This lack of an initial plan probably explains why the volume is not a complete or coordinated work on diseases of the heart and circulation. The individual chapters, with a few exceptions, are authoritative and well written discussions of various aspects of cardiovascular disease. Unfortunately, there is much overlapping of the material presented by different contributors as well as considerable lack of balance with reference to the space allotted to separate subjects. Some of the articles, such as those on "Diseases of the Pericardium," "Chronic Valvular Heart Disease," and "Bacterial Endocarditis," suffer from paucity or absence of illustrations. Each chapter includes a selected bibliography which in many instances is quite extensive.

The volume opens with an informative, fully tabulated essay on the prevalence of heart disease by Haven Emerson. Dickinson W. Richards reviews cardiocirculatory physiology briefly and clearly in the second chapter, and the next 75 pages are devoted to two articles on disease of the pericardium. The second of these is a comprehensive discussion of chronic constrictive pericarditis but this subject already has taken up 12 of the 46 pages of the preceding article. Three papers on congenital heart disease follow. These consist of a reprint of Maude Abbott's chapter in the 1932 edition of the Nelson System, a lucid, up-to-date presentation of the physiology of congenital heart disease by Richard Bing, and a short consideration of the surgical treatment of congenital cardiovascular defects by George H. Humphreys, II. No one will ever question the importance of Maude Abbott's work or challenge her place in medical history but the necessity for including her article in the present volume is open to doubt. Bing fittingly directs attention to her contributions and, in addition to covering recent advances in our knowledge of congenital heart disease, unavoidably repeats much of her treatise. For practical rather than sentimental purposes, Bing's chapter would have sufficed. The section on surgical therapy, although short, reiterates much that is considered in the preceding two chapters and might better have been incorporated in Bing's article.

Rheumatic heart disease is covered in a clear-cut, helpful manner. A part of the material is discussed again in the sections on cardiovascular roentgenology and chronic valvular heart disease. In the latter chapters, also, much of the subject matter of the article on cardiovascular syphilis is encountered a second time. The section on chronic valvular heart disease includes an excellent exposition of the hemodynamic effects of valvular lesions and the mechanism of the resulting physical signs.

Hypertensive vascular disease and its medical and surgical treatment are presented expertly by George A. Perera and Danna W. Atchley. Many, however, will take exception to the suggestion that the term "malignant hypertension" be discarded in favor of the phrase "hypertensive vascular disease in its accelerated or rapidly progressive phase." The succeeding chapter on the surgical therapy of hypertension is an unnecessary repetition.

Only a few more pages are devoted to coronary heart disease than to cardiovascular syphilis. Although myocardial infarction and coronary insufficiency are dealt with thoroughly, the two contributions on these subjects overlap to a considerable degree, and there is no detailed delineation of the syndrome of angina pectoris. Furthermore, the discussion of the medical management of angina pectoris is not adequate and occupies less than a single page. In rather startling contrast, there is a separate chapter of 13 pages on the surgical treatment of this condition.

Pulmonary heart disease, cardiac complications in infectious diseases, and the heart in states of vitamin deficiency are taken up in clearly written, informative summaries. One of the best chapters in the book is that by Richard B. Capps on the hyperactive carotid sinus syndrome. The article on congestive heart failure is complete and practical. The chapter on cardiac neurosis and the one on neurocirculatory asthenia are essentially duplicate discussions.

Clinical electrocardiography is reviewed in a well illustrated section of 96 pages. Much of the text is repeated, to no discernible advantage, in the chapter on abnormal mechanisms of the heart.

There is an instructive paper on arteriosclerosis by E. T. Bell and a good but insufficiently edited article on diseases of the peripheral vascular systems. The latter includes a repetition of the discussion of aortic aneurysm presented earlier in the section on cardiovascular syphilis. It also considers arteriovenous fistula which is the subject of the following chapter by Daniel C. Elkin. The final sections of the volume consist of brief essays on periarteritis nodosa, proliferative endarteritis and lupus erythematosus disseminatus by Franklin T. Hanger.

Although the book does not fulfill the requirements of an integrated text on cardiovascular disease, it must be emphasized that most of the individual contributions have genuine merit. The volume, therefore, can be recommended as a source of collateral reading for medical students and practitioners who wish to extend their knowledge in the cardiovascular field.

A. CARLTON ERNSTENE

L'Insuffisance Cardiaque Chronique. Etudes Physiopathologiques. (Chronic Cardiac Insufficiency. Studies of Pathologic Physiology). *André Cournand, Jean Lequime, and Paul Regniers in collaboration with R. S. Cathcart, H. Denolin, M. I. Ferrer, R. M. Harvey, R. Pannier and D. W. Richards.* Paris, Masson & Cie, 1952. 262 pages, 21 illustrations, 51 tables.

This paper covered monograph, in French, is a product of international cooperation: the first author, a distinguished American scientist of French extraction has done all his medical research in New York, while the other two authors, both Belgians, have worked at Brussels and Gent respectively.

The first part is concerned with "Technics" and contains chapters on cardiac catheterization, on the estimation of cardiac output by many methods, on the measurement of pressures in the greater and lesser circulation and in the cavities of the heart through cardiac catheters, on the estimation of circulation time, of blood volume, and of pulmonary function. These descriptions are detailed and are accompanied by extensive and well chosen bibliographies.

The second part, entitled "Results and Interpretations," is concerned with the physiologic aspects of many circulatory diseases, especially as measured by the Fick cardiac output method with cardiac catheterization, and by right auricular, right ventricular and pulmonary artery pressures taken through cardiac catheters. Results secured by the cardiac output methods available for clinical use before the introduction of the Fick method are not covered by this review.

Various chapters describe the classic physiologic experiments; and the normal regulation of the circulation. They give experimental data concerned with the fundamental physiologic abnormalities of chronic heart and pulmonary disease, in right and left heart failure and in combined failure. Results showing changes induced in the cardiac output and on the pressures in both systemic and pulmonary circulation when therapeutic agents are given to patients suffering from various diseases, are given in great detail. Similar findings in such special conditions as anemia, beri beri, thyrotoxicosis, constrictive pericarditis, and myocardial infarction are also reported.

After describing the technics employed, the results of estimates of the circulation through parts of the body such as the coronary vessels, brain, kidney and liver are also reviewed.

In their theoretic conceptions of cardiac function

he authors are on the conservative side. They uphold the Starling conception against those who doubt its importance in intact animals and in clinical conditions. Their view of cardiac failure coincides with that proposed in 1935 by Harrison.

The book therefore is an exhaustive treatise on the subject of the title, with a most extensive and well chosen bibliography. The field covered has been greatly advanced during the last 20 years and no one has been more conspicuous in leading this advance than the first author, whose personal experience with so much of the subject matter gives the monograph an authority not possessed by most reviews. It is undoubtedly the best thing of its kind known to the reviewer in any language, and he hopes that Dr. Cournand has in mind to translate it into English as he is so eminently competent to do. It is however not a book for practitioners but for experts in the field, and most of these would have no trouble in reading the French edition and, one hopes, would do so with appreciation of the authors' simple, direct and always clear style. And, judging from the papers presented to the First International Cardiological Congress, held in Paris in 1950, there has been great need for a presentation of this field to French speaking medical scientists and practitioners.

Some reservations are inevitable in the early stages of any field, and data concerned with the accuracy of many of the figures given leave much to be desired, but it should be evident to every reader of this book that a large amount of consistent quantitative information has been secured which represents a great advance in our knowledge of the pulmonary circulation in disease. The monograph contains a wealth of information which will be invaluable to all students of the abnormal physiology of cardiovascular disease and the effects of therapy upon it.

ISAAC STARR

Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions (Modern Medical Monographs, No. 3). *Myron Prinzmetal, Rexford Kennamer, Joshua Fields, Eliot Corday, John A. Osborne and L. Allen Smith*, New York, Grune & Stratton, 1952. 120 pages, 49 figures. $4.00.

This monograph presents experimental results which have not previously appeared in print and is a stimulating consolidation of data. In brief, the authors found that electrocardiographic complexes having the same general appearances as the human Wolff-Parkinson-White complex could be produced in dogs in a variety of ways. From a study of a large number of animals the authors feel that the Wolff-Parkinson-White syndrome may be divided into a nodal type and a ventricular type. They postulate that an anomalous anatomic pathway is not necessary for the explanation of this syndrome since they show that the normal intact conduction system is all that is essential to experimentally produce the syndrome. They believe that early excitation of certain portions of the ventricular muscle is due to accelerated conduction by parts of the normal conduction system. One of the most interesting concepts evolved supposes that stimuli arising in localized areas of the ventricles can reflexly produce changes in the conducting qualities of the A-V node.

These concepts, which will require further investigation, should be most stimulating to all persons interested in the physiology of cardiac rhythm and conduction and are much broader than the mere application to the Wolff-Parkinson-White syndrome.

J. SCOTT BUTTERWORTH

Cardiac Emergencies and Heart Failure. Prevention and Treatment. *Arthur M. Master, Marvin Moser, and Harry Jaffe*. Philadelphia, Lea & Febiger, 1952. 159 pages, 13 figures, 4 tables $3.00.

The general practitioner to whom this handbook is directed will find it a useful and authoritative small manual for ready reference.

To cover the subject of prevention and treatment of cardiac emergencies in a few pages is a big order. The authors have approached this task in a workmanlike manner. The various recommended treatments with few exceptions follow currently accepted patterns. They have, perhaps, overemphasized the arrhythmias and slighted congestive heart failure, the condition which the general practitioner is most frequently called upon to treat. It is unlikely that the family physician will be too interested in the electrocardiograms, which are not uniformly clear. The tables on differential diagnosis are very well organized. The one dealing with syncope is particularly good. There are many case reports which for the most part are brief and illustrative. It would make for easier reference if these case reports were more definitely separated from the text and if more subheadings were used throughout the entire book.

The chapter on traumatic heart disease is carefully worded and will give little comfort to those who try to make a "heart case" out of every minor injury to the chest wall.

The difficulties inherent in the early diagnosis of dissecting aneurysm are particularly well presented. There may be some who will disagree with the authors' position in applying anticoagulant therapy to all cases of coronary thrombosis, mild or severe. Others will not agree on the use of adrenocorticotropic hormone (ACTH) in all cases of rheumatic carditis.

Many will applaud the skepticism expressed regarding the efficiency of present day surgical procedures for the relief of angina pectoris.

The index to this little volume has been carefully prepared. The 280 references are well selected.

W. H. BUNN.

The Thoracic Surgical Patient—Preoperative, Anesthetic and Postoperative Care. *Lew A. Hochberg, M.D. Foreword by Frank B. Berry, M.D.* New York, Grune & Stratton, Inc., 1952. 364 pages.

The Thoracic Surgical Patient is not a presentation of surgical technic but deals rather, as the subtitle states, with "Preoperative, Anesthetic and Postoperative Care." The material appears in 13 chapters commencing with pertinent physiology and biochemistry and ending with a section on rehabilitation of the thoracic patient. The remaining chapters discuss the various subspecialties of chest surgery, such as collapse therapy, surgery of the esophagus and cardiovascular surgery.

Including, as this book does, such a wide range of material in a rather short volume, the author is forced for the sake of brevity into a didactic style with the elimination of many points of controversial nature. One exception to this is the chapter on anesthesia which, although concisely written, nevertheless deals fairly completely with the many possible methods and available agents, together with the advantages and dangers of each. The chapter on rehabilitation is also very well written and should prove of real value to those concerned with the care of the thoracic patient.

This book is not intended for the specialist who would desire a much more comprehensive discussion of the field. To one entrusted with subsidiary care of the thoracic patient there is however a great deal of very helpful information which will start him in the right direction. This will have to be supplemented particularly in respect to the problems associated with individual patient variation and to those of children which are largely neglected. This reviewer would have wished for the inclusion of a section on specific nursing care and instruction which is so important to the care of this type of patient.

The style is clear, the book reads easily; it is well edited (although it contains a few inevitable errors) and both the index and the up to date bibliography will prove very valuable to the reader.

ROBERT E. GROSS

Elektrophysiologie des Herzens—Darstellung, Kritik, Probleme. Kreislauf-Buecherei Vol. 11. *K. E. Rothschuh.* Darmstadt, Dr. Dietrich Steinkopff, 1951. 447 pages, 145 figures.

This monograph, written by one of the outstanding German experts on the subject, deals with advances in the electrophysiology of the heart. The presentation is based on the concept of the membrane theory. The fundamental principles of the genesis of action currents under normal and various pathologic conditions are explained in a clear and very instructive way in the first part of the book. In a following section the theory of the electrocardiogram is discussed from the standpoint of a differential as well as vectorial interpretation, and the two theories are compared with regard to their validity and compatibility. The last part deals with electrophysiologic processes underlying disturbances of formation and conduction of the cardiac impulse, and with abnormalities of the electrocardiographic deflections.

Experimental data from the literature are critically reviewed and unsolved problems are pointed out repeatedly throughout the text, both being clarified by many instructive schematic drawings. Unfortunately, at some important points of the presentation, confusion is created owing to a mixup of illustrations and respective legends (figs. 99 and 103), by inconsistencies between text and diagram (fig. 144) and by evident mistakes (p. 320 concerning the effect of electrolytes, and p. 378 concerning primary and secondary T-wave changes). The terminology used by the author to designate various types of electrocardiographic leads is not in accord with that familiar to the American reader. The localization of intraventricular blocks is discussed without consideration of the precordial electrocardiogram. The author favors the theory of a unifocal origin of auricular fibrillation and flutter, and omits completely mention of the re-entry theory in his discussion of the mechanism of premature beats.

This volume is certainly a remarkable, though not always successful, attempt to reconcile different concepts dominating the German and English literature. A revised edition, considering to a greater extent the work of Latin and Anglo-American authors, could represent a standard book on the electrophysiology of the heart.

A. PICK

Syphilis et Lesions Cardio-vascular. *R. Lutembacher.* Paris, Masson et Cie, 1951. 224 pages, 11 figures. 2300 fr.

This book is designed for the pathologist and internist as well as for the syphilographer and cardiologist. Now that many of the late manifestations of syphilis of the cardiovascular system, so common three or four decades ago, have become less frequent, and some even rare, it is good to have a book like this which includes, in considerable detail, a survey of the clinical and pathologic manifestations of the late stage of the disease, as it affects the heart and circulatory system. The illustrative examples of clinical cases, many with autopsy findings, from the vast personal experience of the author are particularly valuable. His ready acceptance of the probable syphilitic origin of a case of mitral stenosis, in a patient in whom the evidence of previous, or existent, rheumatic disease was not obvious, but in whom the existence of syphilis had been proved, is just an illustration of the bias of the author, but does not detract from the value of the book as a whole. Even at this late date in the history of this disease the book can be considered a valuable addition to the subject.

HARRY GOLDBLATT

Blood Clotting and Allied Problems: Transactions of the Fourth Conference January 22–23, 1951. *Edited by Joseph E. Flynn.* New York, Josiah Macy, Jr., Foundation, 1951. 272 pages, 81 illustrations, 27 tables. $4.00.

This fourth in a series of annual volumes brings to the reader almost verbatim the discussions which were held at the 1951 Annual Conference on Blood Clotting and Allied Problems, held under the auspices of the Josiah Macy, Jr., Foundation. This particular conference is the more notable for the addition to the panel of 17 eminent participants of eight guests, including Dr. Helen Payling Wright, of University College Hospital Medical School, London, one of England's foremost "coagulationists."

The discussions center about seven major presentations, the enumeration of which will serve as an index to the content of the volume: Methods for Direct Investigation of Factors Leading to Thrombosis (Knisely); Studies on Canine Hemophilia (Brinkhous); Characteristics of Blood Platelets: Their Significance in Thrombus Formation (Helen Payling Wright); Morphologic and Physiologic Studies of Platelets and Hemostasis (Zucker); Antithrombin—Alpha Tocopherol (Seegers); The Transition of Fibrinogen to Fibrin (Laki); and Polaroscopic Studies of Fibrinogen—Fibrin Reaction (Jaques). Knisely's description of his more recent experimental work concerned with the phenomenon of "sludged blood" and his exposition of views on this provocative phenomenon are of particular interest as is the section devoted to the purported antithrombic action of alpha tocopherol. In this connection, John H. Kay describes at some length his experiences with alpha tocopherol as an index of the thrombosing tendency and as a therapeutic agent for preventing thromboembolism. The critical discussion of the claims advanced by the protagonists are of practical interest to the clinician as well as to the investigator of the clotting mechanism. Particularly striking is the inclusion in this conference of several topics concerned with or related to the morphologic aspects of intravascular clotting, a phase of the general subject which has been relegated to the background during recent years when the physicochemical aspects of coagulation have evoked by far the greater amount of interest. The attention to "sludged blood," to the role of platelets in the formation of thrombi, and to the formation of fibrin indicates a healthy resurgence of interest in the morphology of the blood clot.

While the published accounts of these intriguing conferences are directed primarily to the expert in the field of coagulation, and particularly to the laboratory investigator, any physician who has more than a casual interest in intravascular clotting will find the content of this volume both informative and provocative. As may be said of the transactions of other conferences sponsored annually by the Macy Foundation, the published reports constitute a repository for the most advanced thinking in the particular field.

CHARLES D. MARPLE

Clinical Ballistocardiography. *Herbert R. Brown, Jr., M.D. Vincent de Lalla Jr., M.D., Marvin A. Epstein, M.D., and Marvin J. Hoffman, M.D.* New York, Macmillan, 1952. 188 pages, 138 figures. $5.50.

This monograph represents the first published attempt to summarize the clinically useful information about an instrumental method which began to emerge from obscurity just a little over 10 years ago. In one sense it is long overdue; in another, it represents an almost impossible accomplishment, since the present body of knowledge is so diverse, and has been obtained with such a wide variety of instrumentation.

The authors belong to the high frequency school of ballistocardiography, and have included an excellent chapter on the physical considerations of the instrument. This was written for them by Edgar D. Seymour, Arthur W. Tyler and Miller R. Hutchison of the Development Department of the Eastman Kodak Company. The book is well conceived, clearly written, and profusely illustrated. Since the field of ballistocardiography is so complex and controversial, this reviewer was frankly surprised that he could find little with which to disagree.

JOHN R. BRAUNSTEIN

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Although the two articles which follow have been published in *Modern Concepts of Cardiovascular Disease*, they are being reprinted in Circulation because it is felt that their timeliness and importance justify their being given wide publicity. The authors constitute special committees appointed for the preparation of this material by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

THE PROTECTION OF RHEUMATIC FEVER PATIENTS CARED FOR ON THE WARDS OF GENERAL AND CHILDREN'S HOSPITALS*

By Edwin L. Harmon, M.D., Chairman, Homer F. Swift, M.D., Frederick J. Lewy, M.D., Dora E. Young, B.B.A., and Marjorie T. Bellows, M.S.

Because questions frequently arise in connection with the protection of rheumatic fever patients in general and children's hospitals, the following statements intended to guide such hospitals are issued by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. They should be regarded as embodying certain principles which an individual hospital may apply in its effort to achieve protective measures.

1. Attacks of rheumatic fever frequently follow group A streptococcal infections– usually of the upper respiratory tract.

2. Persons who have recovered from an attack of rheumatic fever or who have rheumatic heart disease, even though the rheumatic fever may be quiescent, are especially liable to develop a recurrence of the disease if they contract a group A streptococcal infection. Moreover, a new rheumatic attack may be induced in a patient in the subacute active stage if he contracts a new infection with group A hemolytic streptococci of a serological type, or types, different from that which previously infected him.

3. The introduction of rheumatic fever patients into hospital wards or other environments, such as outpatient departments, where group A streptococcal carriers may be encountered, exposes them to hazards which should be avoided. To the extent that is reasonably possible in the individual institution, protection of such patients from contact with other patients, visitors or employees suffering from such hazardous infections should be practiced.

Patients suffering from scarlet fever, erysipelas, or acute glomerular nephritis may be considered specially dangerous even without further laboratory confirmation of type of organism involved. Sore throat or acute tonsillitis, especially when associated with exudates, distinct fever, and leucocytoses, may ordinarily be considered almost as dangerous. Milder upper respiratory infections are also dangerous. Dust and lint from bedding, handkerchiefs, and clothing in the immediate environment of a person who is expelling streptococci from his mouth or nose are potent sources of infection, as are also dishes and other utensils he uses.

4. Susceptible rheumatic fever patients while in dangerous environments such as open wards should receive treatment (chemotherapeutic or antibiotic drugs) that will markedly decrease their liability to contract such streptococcal infections. Furthermore, it is possible by suitable protective measures to render their environments comparatively free from danger of

* The term "Rheumatic Fever" is considered to include rheumatic fever and rheumatic heart disease.

reinfecting them with group A hemolytic streptococci. For suggested appropriate individual treatment see Section below.

5. To the fullest extent possible within the laboratory facilities of the hospital, or those available to the hospital, all reasonable efforts should be made to determine the presence of group A streptococci among patients or personnel of the ward and to deal appropriately with such cases when the organism is identified.

6. Mindful of the above facts and recognizing that in the average general hospital environment complete communicable disease ward precautions and techniques for the protection of the rheumatic fever patient are neither possible nor psychologically desirable, the hospital caring for such patients should nevertheless, institute procedures and measures which will protect such patients. Detailed protective procedures should be developed by the individual institution through the collaboration of the appropriate responsible members of the medical, pediatric and laboratory staffs, Nursing Department and Administration.*

In developing protective measures which will in effect better protect the rheumatic fever patient from his environment and not others from him, strong emphasis should be placed on appropriate education of the patient, the family and hospital workers who are in regular or casual contact with rheumatic fever patients.

Appropriate Individual Treatment (Chemotherapeutic or Antibiotic Drugs)

The following outline of appropriate treatment of the patient and streptococcal carriers in his environment may be considered adequate:

1. *Protecting the patient against streptococcal infections by*
   (a) Daily oral administration of small doses (0.5 to 1.0 gm.) of relatively non-toxic sulfonamides,
   or
   (b) Daily oral administration of 200,000 units of buffered penicillin G divided into two doses and given on an empty stomach. Other antibiotics may have a similar prophylactic influence and may be employed, but more experience is available with penicillin.
2. *Reducing the danger arising from other patients with streptococcal infections or from carriers of Group A hemolytic streptococci*
   (a) This can be effected by giving large doses of penicillin, or other antibiotics for a period of ten days to those patients who are expelling streptococci. Such attempted elimination or diminution of the carrier state with respect to hemolytic streptococci should be bacteriologically controlled if possible.
   (b) Patients who have been in contact with a known case of streptococcal infection should be treated in the same way as those with streptococcal infections.
3. *Attempting to cure streptococcal infections in a rheumatic fever subject early in the course of such an infection by intensive antibiotic therapy, started promptly and continued for 10 to 14 days.*

   Prophylaxis of the rheumatic attack is probably most effectively attained by intramuscular administration of an antibiotic drug. It can also often be effected by oral administration of one million units of buffered penicillin G daily, divided into four equal doses given on an empty stomach. Rheumatic fever patients so treated should be carefully studied both clinically, and by suitable laboratory and electrocardiographic techniques, to ascertain whether rheumatic sequelae have been really prevented or only reduced to a sub-clinical level.

* Those seeking detailed communicable disease protective procedures from which to pattern specific procedures may well refer to "The Control of Communicable Diseases in Man," American Public Health Association, Seventh Edition, 1950, and "Guide for the Handling of Communicable Diseases in Hospitals, New York State Department of Health, 1950.

PREVENTION OF RHEUMATIC FEVER

By BURTIS B. BREESE, M.D., CHAIRMAN, MARJORIE T. BELLOWS, M.S., EDWARD E. FISCHEL, M.D., ANN KUTTNER, M.D., BENEDICT F. MASSELL, M.D., CHARLES H. RAMMELKAMP, M.D., AND EDWARD R. SCHLESINGER, M.D.

Rheumatic Fever is a recurrent disease which can be prevented. It is now generally agreed that both the initial and recurrent attacks of the disease are usually precipitated by infections with beta hemolytic streptococci. Therefore, the prevention of rheumatic fever and rheumatic heart disease depends upon the control of streptococcal illnesses. This may be successfully accomplished by (1) early and adequate treatment of streptococcal infections in all individuals and (2) prevention of streptococcal infections in rheumatic subjects.

I. TREATMENT OF STREPTOCOCCAL INFECTIONS

In the general population at least 3 per cent of untreated streptococcal infections are followed by rheumatic fever. Among certain individuals, especially those with previous rheumatic fever, the incidence is much higher. Adequate and early penicillin treatment, however, will prevent most attacks of rheumatic fever and eliminate streptococci from the throat.

A. Diagnosis of Streptococcal Infection

In most instances it is possible to recognize streptococcal infections by their clinical manifestations but laboratory tests may assist in establishing the diagnosis.

1. Epidemiology

The seasonal pattern and presence of similar cases in the community or household may be helpful. For example, streptococcal infections in the northern United States are most common from January through June. Likewise, a case of scarlet fever in one child would suggest that a sore throat in another has the same etiology.

2. Symptoms

a. Sore throat—onset sudden, in the tonsillar area, not in the trachea.

b. Headache—common.

c. Fever—variable—but generally from 101 to 104 F.

d. Abdominal pain—common, especially in children. Not too common in adults, but does occur.

e. Nausea and vomiting—common, especially in children.

f. These symptoms are usually *not* present: (1) simple coryza, (2) cough, (3) hoarseness.

3. Signs

a. Red throat—frequently beefy red, but if seen early the redness may be mild.

b. Exudate—usually present.

c. Glands—swollen, tender tonsillar glands at angle of jaw.

d. Rash—scarlatiniform (characteristic of scarlet fever—not common).

e. Discharge—otitis media and sinusitis indicated by (serous or purulent) aural or nasal discharge are frequent complications of streptococcus pharyngitis.

4. Laboratory

a. White blood count—generally over 12,000 and in children frequently over 20,000.

b. Throat culture—positive for hemolytic streptococci.

5. Therapeutic Response

Almost without exception patients with streptococcal infections are vastly improved within 24 hours after penicillin has been started and the temperature normal, or nearly so.

This therapeutic response is characteristic and if it does not occur, the chances are much against the disease being due to hemolytic streptococci.

B. Treatment of Streptococcal Infections

In order to be effective, treatment should be started immediately when a streptococcal infection is suspected and continued for sufficient time to eradicate the streptococci from the throat.

Penicillin is the drug of choice for treating streptococcal infections.

Both the oral and the intramuscular routes

of administration have been utilized successfully for penicillin therapy of streptococcal infections. Intramuscular injections have been proved to prevent rheumatic fever. The data on the value of oral penicillin as a preventive is less complete.

Oral administration in comparison with intramuscular administration has these advantages: (1) It is not as distasteful to many patients. (2) It requires fewer physician visits.

It has these disadvantages: (1) Larger amounts of penicillin must be used. (2) It is difficult to administer to vomiting or refractory children. (3) In some adults it gives rise to persistent diarrhea and pruritus ani. (4) It is difficult to be sure that treatment is continued for sufficient time and given in proper relation to meals to be effective.

1. Recommended Treatment Schedules

a. Intramuscular Penicillin: (1) *Children*—one intramuscular injection of 300,000 units of procaine penicillin with aluminum monostearate in oil *every third day for three doses.* (2) *Adults*—one intramuscular injection of 600,000 units procaine penicillin in aluminum monostearate *every third day for three doses.* (Note: Less preferable, but usually effective—two doses as above at three day intervals.)

b. Oral Penicillin: (1) First five days: 200,000 to 300,000 units one half to one hour before meals and at bedtime (total of 800,000 to 1.2 million units per day in 4 divided doses. The lesser amount for children, the larger amount for adults). (2) Second five days: 200,000 to 250,000 units one half to one hour before meals. (Total 600,000to 750,000 units per day in 3 divided doses.)

Note: To be effective, therapy should be continued for the entire ten days even though the temperature may return to normal and the patient may feel better within one or two days.

c. Combination of Intramuscular and Oral Penicillin: Therapy may be begun with one injection of penicillin (300,000 units procaine penicillin with aluminum monostearate in oil) and then, beginning three days after the injection, continued for an additional seven days with oral penicillin according to the schedule in (2) outlined above.

d. Other Medication. (1) Aureomycin is less effective than penicillin in controlling streptococcal infection but is especially useful in those sensitive to penicillin. *Dosage:* Total 10 mg. per pound of body weight in four divided doses daily for two days. Cut dose in half for remaining eight days of therapy.

(2) New preparations of penicillin: These may be effective and even preferable to the treatment schedules outlined, but at present they have not had sufficient trial to warrant their recommendation.

(3) Other antibiotics: At present there is inadequate data on their value.

e. Not Recommended for Treatment: (1) Penicillin troches or lozenges. (2) Penicillin followed by sulfonamides. (3) Sulfonamide drugs.

(Note: Recurrences of streptococcal infection should be treated as primary attacks.)

II. Prevention of Streptococcal Infections

A. General Rules for Prophylaxis

1. Who should be treated?

All individuals under the age of eighteen who have had rheumatic fever or chorea and all those over this age who have had an attack within five years.

2. When should prophylactic treatment be initiated?

At the end of the second week of the attack of rheumatic fever or any time thereafter when the patient is first seen.* Prior to the start of prophylaxis, beta hemolytic streptococci should be eradicated by proper treatment of the patient. (See methods of penicillin therapy recommended above.)

3. How long should prophylaxis be continued?

In children, at least to the age of eighteen; in all those above this age, for at least five years from their last attack.

4. Should prophylaxis be continued during the summer?

Yes.

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* *Note:* In patients receiving ACTH or Cortisone, be cautious that other infections are not masked since the prophylactic dose is inadequate to treat such concurrent illnesses as pneumonia or meningitis.

B. Prophylactic Methods

1. Sulfadiazine

This drug has the advantage of being easy to administer, inexpensive and effective (other newer sulfonamides are probably equally effective). Although resistant streptococci have appeared during mass prophylaxis in the armed forces, this is rare in civilian populations.

a. Dosage—from 0.5 to 1.0 Gm. taken each morning throughout the year. The smaller dose is to be used in children under sixty pounds.

b. Toxic Reactions—these are infrequent and are usually minor. However, in any patient being given prophylaxis with sulfonamides consider all rashes and sore throats as possible toxic reactions to the drug, especially if they occur in the first eight weeks of prophylaxis. The chief toxic reactions are:

(1) Skin eruptions: (a) Morbilliform—much like measles—continue drug with caution. (b) Urticarial—best discontinue treatment. (c) Scarlatiniform—often associated with sore throat and fever. Unsafe to continue drug.

(2) Blood reactions: Leukopenia—Discontinue if white blood count falls below 4,000 and polynuclear neutrophiles below 35% because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white blood counts are advisable for the first two months of prophylaxis. (The use of sulfonamides therapeutically for any reason in this period should be preceded by a white blood count.) The occurrence of agranulocytosis after eight weeks of continuous prophylaxis with sulfonamides is extremely rare.

2. Penicillin

Although experience with oral penicillin for the prophylaxis of rheumatic fever is more limited than that with the sulfonamides, the antibiotic promises to be a safe and effective prophylactic agent. Oral penicillin has the desirable characteristics of being bactericidal for hemolytic streptococci and of rarely producing serious toxic reactions. It has the disadvantages of being more costly than sulfadiazine and because of the need of giving it on an empty stomach, of being somewhat more difficult to administer.

Oral penicillin represents an alternative drug for rheumatic fever prophylaxis. It is especially important to use this agent for those who do not tolerate sulfadiazine.

a. Dosage: Although other routines of administration may prove satisfactory, the following schedules are suggested:

200,000 to 250,000 units two times daily is recommended. Since penicillin is best absorbed on an empty stomach, the time of administration should be ½ to 1 hour before a meal or at bedtime. A single dose of 200,000 to 250,000 units before breakfast is less preferable.

b. Toxic reactions: (1) Urticaria. (2) Reactions similar to serum sickness—they include fever and joint pains and may be mistaken for rheumatic fever. (3) Angioneurotic edema—although many individuals who have had reactions to penicillin can subsequently take the drug without trouble, it is safer not to use penicillin, if the reaction has been severe and particularly if angioneurotic edema has occurred.

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NEW DIET MANUAL

The American Heart Association and its affiliates have issued a new, comprehensive diet handbook, *Food for Your Heart*, for use by physicians in the dietary management of heart patients. The manual incorporates nine diets, sample menus, and the latest information on nutrition and heart disease. The manual also dispels many misunderstandings about reducing and special diets, and makes clear the reasons why only physicians should prescribe such diets for patients.

Endorsed by the American Medical Association's Council on Foods and Nutrition, the new guide states that proper diet counts in the prevention and treatment of many kinds of heart disease, hypertension, and of some complications, such as edema.

Food for Your Heart was prepared by the staff of the Department of Nutrition, Harvard School of Public Health. Dr. Fredrick J. Stare, Chairman of the Department, headed a special committee of the American Heart Association, composed of authorities in the field, which supervised the preparation of the handbook.

The diet manual may be obtained by laymen from affiliated heart associations only on doctor's prescription. It will also be distributed to physicians, nutritionists, nurses, dieticians, health departments, and hospitals.

The manual is tab-indexed for quick reference. Desirable weights and how to reach them, cholesterol and heart disease, sodium and heart disease, and general dietary principles are discussed. Low sodium diets are so arranged in the manual that the physician has only to mark the diet he wishes the patient to follow, and to indicate the list of foods from which the patient may choose for the day. These foods are listed according to weight and composition (fat, carbohydrate, and protein content), as well as varying levels of sodium restriction, so that the physician will have no difficulty in making quick adjustments in the patient's diet, if he so desires. A pocket on the inside cover may be used by the physician for additional instructions to the patient.

The booklet may be obtained from affiliated Heart Associations or from the American Heart Association.

INTERNATIONAL CARDIOLOGICAL CONGRESS

The Organization Committee for the Second International Congress of Cardiology has held its first meeting in New York under the Chairmanship of Dr. Paul D. White, who will serve as President of the Congress. Co-Chairmen of the Committee are Dr. James L. Watt, Director of the National Heart Institute of the U. S. Public Health Service, and Dr. Irving S. Wright, President of the American Heart Association.

The Congress has been tentatively set for the week of September 12, 1954. Scientific Sessions will be held in Washington, D. C., and Bethesda, Md. Demonstrations and visits to exhibits are planned for the Washington area and special features will be scheduled in various other cities. The Committee also discussed the possibility of commercial exhibits.

The Committee membership includes representatives of the Armed Forces as well as officers and members of the Association and the Public Health Service.

AMERICAN SOCIETY FOR STUDY OF ARTERIOSCLEROSIS

The seventh annual meeting of this Society will be held Nov. 1 and 2, in Chicago. Factual 200 word abstracts on papers for this meeting

must be submitted by May 30. Dr. Louis N. Katz, Michael Reese Hospital, Chicago 16, Illinois, is Program Chairman, and Dr. O. J. Pollak, P. O. Box 228, Dover, Delaware, is Secretary.

ANNUAL MEETING RESERVATIONS

All those planning to attend the American Heart Association's Annual Meeting and Scientific Sessions at the Hotel Chelsea, Atlantic City, April 8–12, may obtain hotel reservation forms from the Association. Reservations should be mailed *directly* to the hotel in Atlantic City at the earliest possible date. The same hotel reservation form may be used by those desiring to attend the meetings of both the American Heart Association and the American College of Physicians.

MEETINGS

Mar. 1–7: 14th International Congress of Military Medicine and Pharmacy, Montevideo, Uruguay. Secretary, Dieccion General del Servicio de Sanidad Militar, Avenida 8 de Octubre No. 3040 esquina Mariano Moreno, Montevidio, Uruguay.

Apr. 8–12: Twenty-Ninth Annual Meeting, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 8–9: Assembly panels, Assembly meeting of the Scientific Council, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 10–12: Twenty-Sixth Scientific Sessions, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 13–17: American College of Physicians, 34th Annual Meeting, Hotel Haddon Hall-Chalfonte, Atlantic City, N. J.

Apr. 20–22: Areal Meeting, American Academy of Pediatrics, Hotel Statler, Boston, Mass. Executive Secretary, E. H. Christopherson, M.D., American Academy of Pediatrics, 610 Church Street, Evanston, Ill.

Apr. 23–25: 1st Western Hemisphere Conference of World Medical Association, Richmond, Va. Secretary-General, Dr. Louis H. Bauer, World Medical Association, 2 East 103rd Street, New York 29.

May 7–10: National Congress of Cardiology, Sevilla, Spain. Secretary, Dr. E. Benot, 3 Paseo de las Delicias, Sevilla, Spain.

May 15–16: Annual Spring Meeting, Council for High Blood Pressure, Cleveland, Ohio.